VOL. 35 DECEMBER 1959 NO. 12

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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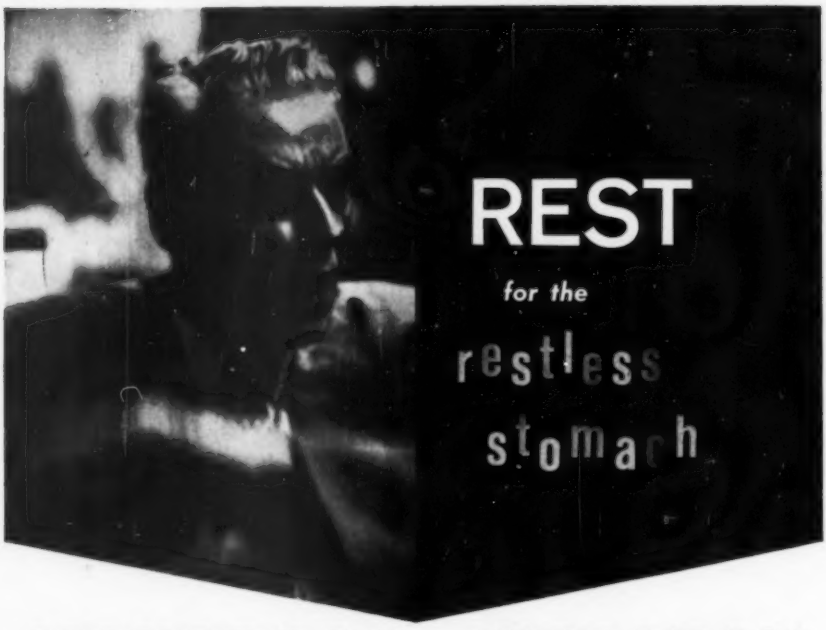

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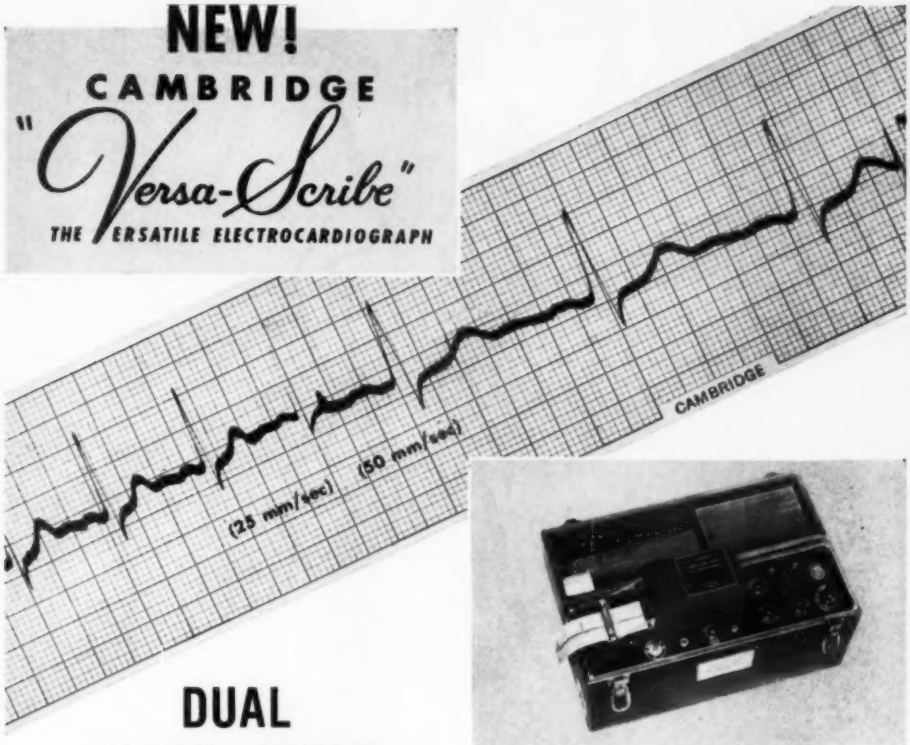

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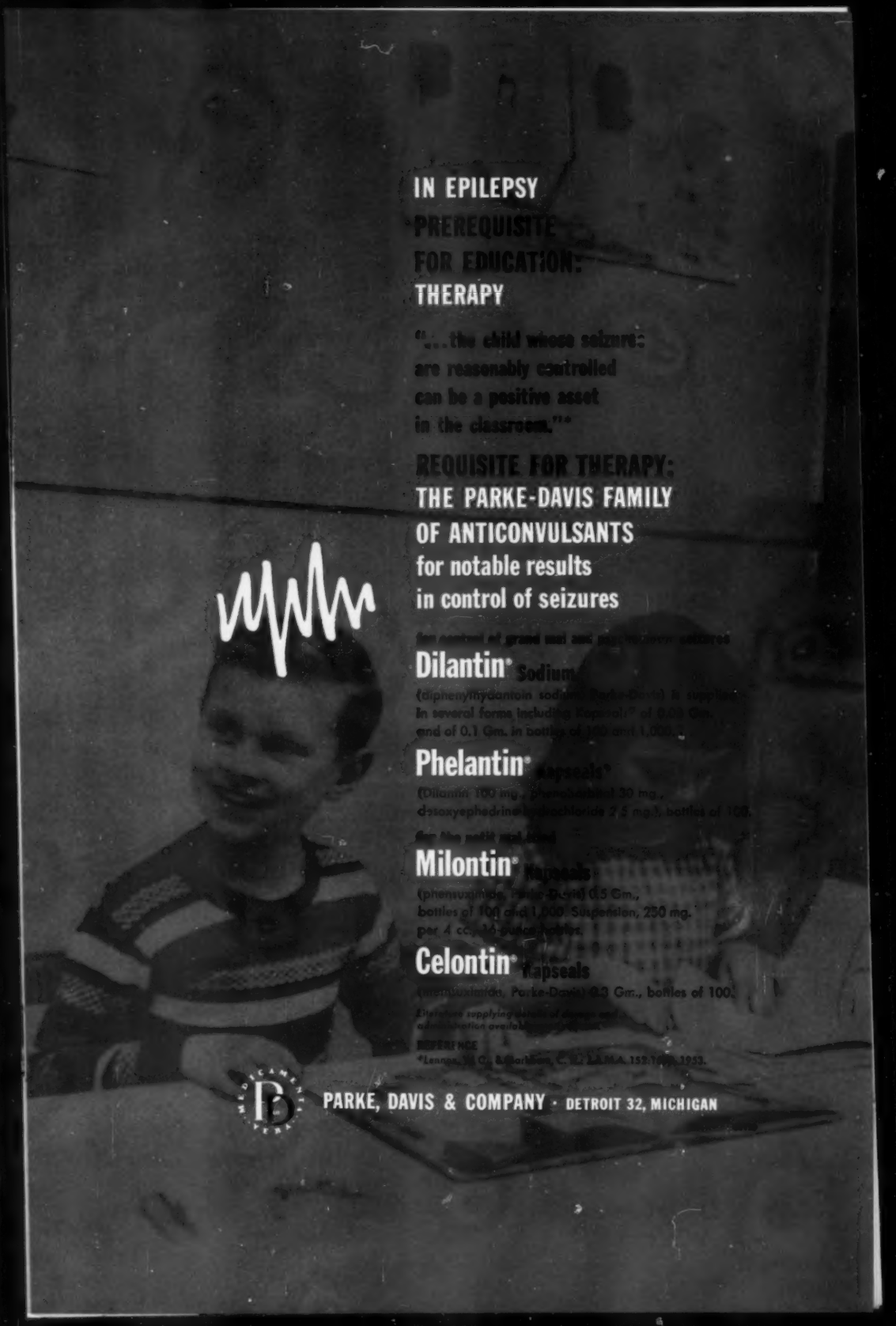
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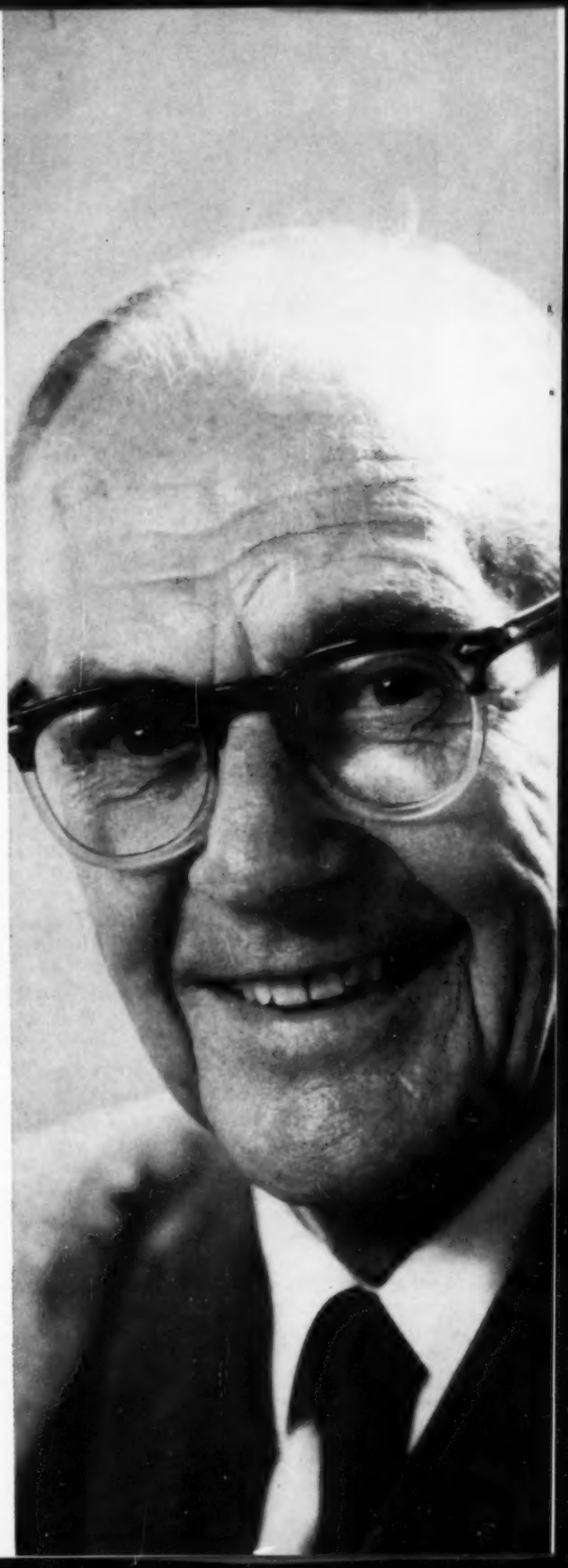

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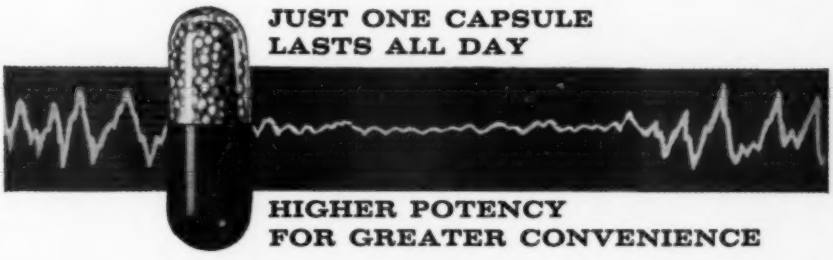

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BULLETIN OF
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VOL. 35, NO. 12 DECEMBER 1959

JAUNDICE AND BILIRUBIN METABOLISM*

RUDI SCHMID

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I would like to review briefly some of the newer concepts of bile pigment metabolism and then discuss two more specific problems which are presently under intensive investigation.

The average life span of the normal human erythrocyte is 120 days[1]. At the end of this period, the red cells are destroyed, and the hemoglobin is broken down. Of the three hemoglobin constituents, the iron is almost completely reutilized for formation of other iron-containing compounds[2], and the globin is degraded and returned to the body pool of amino acids[1]. On the other hand, the protoporphyrin is not preserved, but the porphyrin ring is opened, and the resulting bile pigments are excreted[3, 4]. The exact nature and the sequence of the individual steps in hemoglobin catabolism are still

* Presented at the Postgraduate Week, *Research Contributions to Clinical Practice*, The New York Academy of Medicine, October 16, 1958. Manuscript received April 1959.

From the Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts.

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a matter of controversy[5]. The opening of the porphyrin ring occurs in one of the methene-carbon bridges and results in formation of a straight chain of four pyrrole rings, which is the basic structure of bilirubin and of most other bile pigments[6].

Bilirubin is not only produced from catabolism of hemoglobin, but also from breakdown of other heme proteins, such as myoglobin, catalase, cytochromes, proxidase and others[6]. Moreover, it has been observed that an additional fraction of bile pigment is formed from other sources, the nature of which is not yet clear[7, 8]. On the other hand, there is at least indirect evidence to suggest that bilirubin and the pigments and chromogens resulting from its bacterial reduction in the intestines may not be the only metabolites formed on degradation of heme-containing proteins, although they undoubtedly represent the most important end-products[5].

Bilirubin, which is water-insoluble, is carried in the plasma by means of its attachment to proteins, of which albumin is probably the most important; but other plasma proteins have also been shown to bind the pigment[9]. Further work is needed to clarify the relative importance of the various plasma protein fractions in the transport of *physiological* amounts of bilirubin in the blood. The same is true of the mechanisms by which the pigment is carried into the liver cells to the site of the enzymatic apparatus, which catalyzes the conjugation. It may be that a better understanding of these transport mechanisms would help to clarify the pathogenesis of some of the forms of chronic hyperbilirubinemia.

In the liver, bilirubin is converted into water-soluble forms. This is achieved by conjugation with hydrophilic compounds, of which glucuronic acid is the most important[10, 11] (Figure 1). Glucuronide formation is an enzymatic process in which the carbohydrate moiety is derived from uridine diphosphate glucose by a dehydrogenase reaction[12]. Many tissues have the ability to form glucuronides[13], but for bilirubin, the liver is probably the most important organ to do so. It should be noted that in this biosynthetic reaction only the uridine nucleotide, but not free glucuronic acid, can serve as a substrate[12, 13]. In the bile, most of the bilirubin is excreted as a diglucuronide, but some may also be present as a monoglucuronide.

A small fraction of the bilirubin in human bile is excreted in the form of the sulfate[14]. This is not surprising, since for most compounds

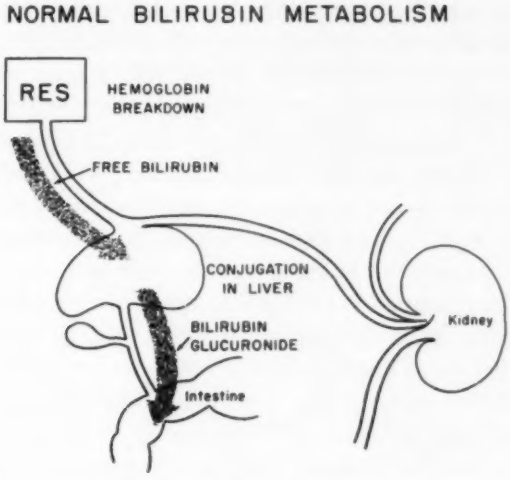

Figure 1—Bilirubin metabolism under normal conditions.

which form conjugates, this can occur in more than one way. However, one pathway is usually predominant, and for bilirubin this appears to be formation of a glucuronide.

As has been noted above, bilirubin is almost insoluble at the pH of the plasma, whereas conjugated bilirubin is water-soluble. This difference in solubility probably accounts for the indirect and the direct reactions which these two forms of the pigment give with the van den Bergh reagent[10, 11].

However, because of the kinetics of the reaction involved[15], and because of the presence of solubilizing substances in the plasma, the van den Bergh reaction does not permit more than an approximation of the concentration of the two pigment types[11]. For clinical purposes this is usually satisfactory, but for biochemical investigations, more elaborate methods of separation, purification and estimation are required. In the original studies which led to the recognition of direct-reacting bilirubin as bilirubin glucuronide, the two pigment fractions were converted to their respective and more stable azo derivatives. On the basis of their differing solubilities, the two derivatives could be separated by countercurrent distribution[10], or by paper chromatography[11]. Hydrolysis of the

azo derivative of bilirubin glucuronide resulted in formation of the azo derivative of non-conjugated bilirubin and of free glucuronic acid.

In hemolytic anemia, the over-production of bilirubin which results from the increased breakdown of hemoglobin appears to exceed the capacity of the liver to conjugate and excrete the pigment. This results in retention of non-conjugated bilirubin in the plasma, giving a predominantly *indirect* van den Bergh reaction, while bilirubinuria is absent. It is not known whether the rate-limiting factor lies in the conjugating enzyme system itself, or possibly in the mechanisms responsible for the transport of bilirubin into the liver cells.

A different situation is present in obstructive jaundice. Here, the plasma contains largely conjugated bilirubin, giving a predominantly *direct* van den Bergh reaction, and bilirubinuria is present. In hepatitis and cirrhosis, the plasma often contains both bilirubin and conjugated bilirubin, and bilirubinuria is usually present. Thus, as far as pigment metabolism is concerned, these conditions frequently appear to exhibit an obstructive component, but the explanation for this phenomenon is not clear and must await further studies, particularly on the fine structure of the liver. It has been observed, however, that in disturbances believed to involve mainly the parenchymal cells of the liver, the plasma may contain a relatively large fraction of bilirubin monoglucuronide[16]. This may suggest that a reliable and simple method for the separation and estimation of bilirubin mono- and diglucuronide might be of considerable diagnostic significance for the distinction between parenchymal and obstructive forms of icterus.

In the short time which remains, I would like to discuss two more specific and somewhat controversial problems.

As has been mentioned before, glucuronide formation is an enzymatic process in which the glucuronic acid is transferred from the uridine nucleotide to the accepting substrate[12]. The available evidence indicates that in its free form, glucuronic acid cannot be used directly for glucuronide formation[12]. On the other hand, it has been shown that glucuronic acid is an intermediate in one of the glycolytic pathways[17]. If experimental animals are fed this compound containing an isotope, a fraction of it is absorbed and metabolized, and the label may appear in various other carbohydrate fractions. This probably explains the observation that, after administration of isotopically labelled glucuronic acid, a small fraction of the label may appear in glucuronides excreted in

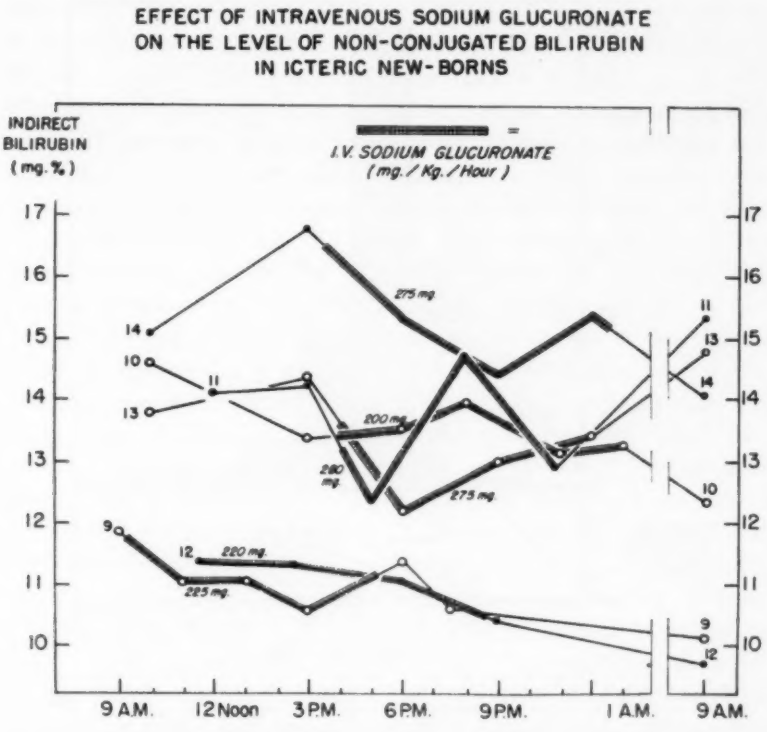

Figure 2—At the third neonatal day, six premature infants with marked jaundice were given sodium glucuronate by intravenous drip. Individual doses are given in mg. per kg. per hour, and the total duration of the administration is indicated by heavy bars[20].

the urine[18]. This finding does not indicate that glucuronic acid was *directly* incorporated into glucuronides, but it merely suggests that part of the administered compound was metabolized, which resulted in labelling of the carbohydrate pool, including the uridine nucleotide of glucuronic acid.

There is thus little experimental basis for the belief that, *in vivo*, the rate of glucuronide formation could be augmented by administration of glucuronic acid, as has been suggested[19]. We have been unable to confirm the reports by Danoff, Boyer and Holt[19] that, in newborn infants with hyperbilirubinemia, administration of large amounts of

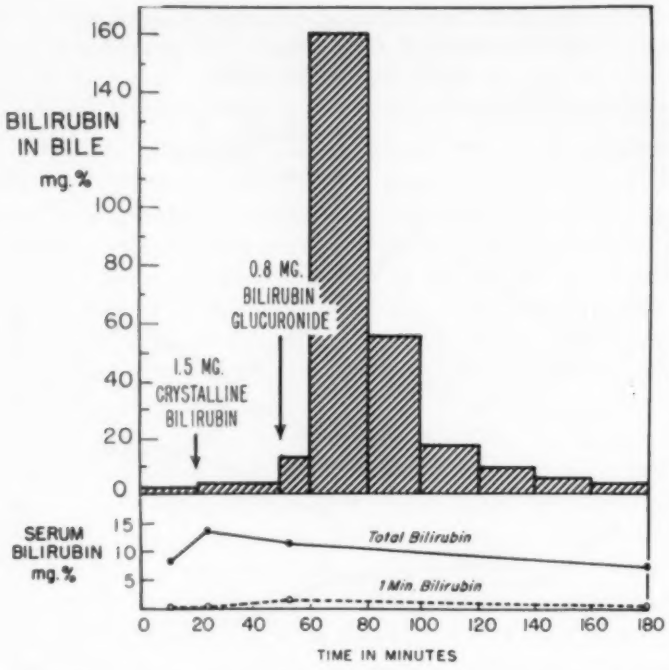

Figure 3—In a rat with congenitally defective glucuronide formation, the bile duct was canalized and the bile was collected for bilirubin determination. At the times indicated by arrows, bilirubin and conjugated bilirubin respectively were injected by intravenous route[20].

glucuronic acid may reduce the serum bilirubin levels[20]. As seen in Figure 2, in six premature infants with neonatal icterus, who were given glucuronic acid by intravenous route at a rate of approximately 200 mg. per kg./hr. for a period of eight hours, no significant decrease in serum bilirubin concentration could be observed[20]. Similar negative results have been obtained with oral administration of this compound[20].

A decisive factor in causing the transient hyperbilirubinemia during the neonatal period appears to be the inadequate development of the glucuronyl transferase system[21, 22]. During the intra-uterine period, the bilirubin formed in the fetus is probably transferred through the placenta to the mother's circulation[23]. At birth, however, this route is interrupted and the pigment formed has to be conjugated and excreted

by the newborn organism. During the immediate neonatal period, the efficiency of this mechanism is low, which frequently leads to retention of nonconjugated bilirubin in the plasma. After the first few days of life, as the glucuronide-forming system reaches its full capacity, the bilirubin level gradually returns to normal values. Attempts to induce increased enzymatic activity before birth have so far remained unsuccessful[23]. For the time being, exchange transfusions are the only means of preventing dangerous levels of serum bilirubin concentrations.

Another problem which I would like to discuss briefly is the *pathogenesis* of some of the syndromes which are associated with chronic nonobstructive hyperbilirubinemia. In these instances, retention of nonconjugated bilirubin in the plasma occurs in the absence of biliary obstruction, or a significant degree of hemolysis. Such a syndrome is present in a mutant strain of Wistar rats, which originally was studied by Gunn[24] and by Malloy and Loewenstein[25]. These rats exhibit a marked reduction in the rate of glucuronide formation both *in vivo* and *in vitro*[26]. Their bile contains only very small amounts of bilirubin, and fecal excretion of urobilinogen is greatly reduced[26], but Cholografin and Bromsulphalein are freely excreted. As seen in Figure 3, bilirubin, if injected intravenously, is not excreted in the bile, whereas injection of conjugated bilirubin is followed by a rapid and large increase in bile pigment concentration. These observations confirm and extend Malloy and Loewenstein's original suggestion that, in these rats, the hyperbilirubinemia is the result of an inability to convert bilirubin into its water-soluble form, suitable for excretion.

A similar syndrome in children was first described by Crigler and Najjar[27] in 1952. Such patients exhibit severe congenital icterus, which frequently is associated with life-endangering disturbances of the central nervous system[27]. The plasma contains high concentrations of nonconjugated bilirubin, but bilirubinuria is absent[28]. Bile contains little bilirubin and fecal urobilinogen excretion is greatly reduced[28]. Impaired glucuronide formation and excretion has been demonstrated with a variety of compounds which normally form glucuronides, including N-acetyl-p-aminophenol (NAPA), tetrahydro-hydrocortisone, salicylates and menthol[29, 30]. This rare syndrome undoubtedly is of congenital nature, but little is known of its mode of inheritance.

The demonstration of a defect in glucuronide formation in these patients with marked chronic icterus suggested the possibility that a

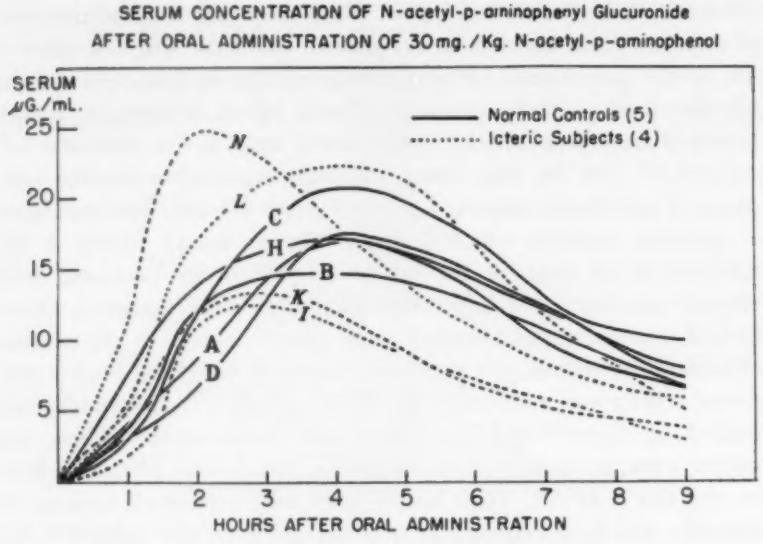

Figure 4—Four male patients with mild chronic hyperbilirubinemia and five normal subjects were given a single oral dose of 30 mg./kg. N-acetyl-p-aminophenol. The serum concentration of the glucuronide was determined after 1, 2, 4, 7 and 9 hours[32].

similar, but less severe impairment of glucuronyl transferase activity might account for the mild hyperbilirubinemia present in constitutional hepatic dysfunction or so-called Gilbert's disease[31]. In several of these patients, however, studies *in vivo* failed to reveal a demonstrable reduction in their ability to form glucuronides[32]. As seen in Figure 4, administration of a single oral dose of NAPA resulted in serum concentrations of NAPA glucuronide which showed little difference between control subjects and patients with mild hyperbilirubinemia. The interpretation of these findings is complicated by the fact that it is not yet known whether a single or several related enzyme systems catalyze the formation of different types of glucuronides. If different enzymes with a high substrate specificity are involved, the possibility cannot be excluded that in Gilbert's disease only that enzymatic mechanism is impaired which is responsible for formation of bilirubin glucuronide. However, as an alternative explanation, the possibility should be considered that not the conjugating mechanism, but the rate at which the pigment

can reach the site of the enzymatic apparatus in the cells may be the limiting step responsible for the retention of pigment[32]. This possibility deserves further exploration, as it is apparent that the nature of the disturbance in this syndrome is still unclear.

In the last few years, some advances have been made in the field of bilirubin metabolism, but a number of new problems have arisen which now await solutions. The many studies which are being carried out in various laboratories throughout the world are expected to provide some of the answers to the questions which I have discussed this evening.

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ELECTROGASTROGRAPHIC AND RADIOLOGIC STUDIES IN PATIENTS POSTGASTRECTOMY*

EDMUND N. GOODMAN, HENRY COLCHER and RALPH SCHLAEGER

THIS is a report on a coordinated radiological and electrogastrographic study undertaken in a group of 65 postgastrectomy patients to obtain some data on the mechanism of gastric emptying and the electrical behavior of the gastric remnant and adjoining small intestine. The material is presented according to the techniques employed.

ELECTROGASTROGRAPHIC OBSERVATIONS

The method of obtaining recordings of the electrical activity of the stomach and small intestine has been described by us[1, 2]. In brief, a small rubber balloon is mounted on a triple lumen tube (Figure 1). Five silver discs, 4 mm. in diameter, are applied to the balloon in such a manner as to make a one millimeter contact with the gastric or intestinal mucosa when the balloon is inflated. The electrode leads pass through one of the lumens. A sixth electrode consists of a chloridized silver bead contained in a small glass receptacle filled with saline and plugged with cotton. Electrical contact with the mucosa is made through this saline medium. The lead passes through a second lumen. A larger, but essentially similar, electrode is applied to the forearm. The potentials from several sites are recorded simultaneously with reference to this arm electrode. The balloon is inflated in the stomach or intestine with approximately 100 ml. of air introduced through holes in the third lumen. It is connected to a Statham gauge for recording intraluminal pressure changes.

In our study, the electrical output of the Statham gauge was recorded

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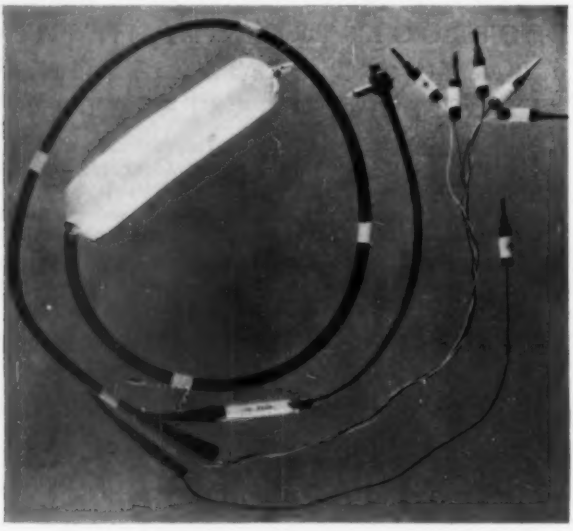

Fig. 1—Triple lumen tube with balloon and six electrodes.

simultaneously with the electrogastrogram. The equipment consisted of a 6 Channel Offner amplifier modified with preamplifiers designed to provide the necessary high input resistance, high in-phase rejection and low drift. These preamplifiers are interchangeable for pressure measurements using Statham gauges or potential measurements using electrodes. The location of each electrode was established radiologically.

The electrogastrogram, developed by our group, is essentially the recorded measurement of gastric potentials. It has been used in recent years, clinically and experimentally, in anesthetized and unanesthetized animals. The method has been applied to measuring potentials at various levels of the gastrointestinal tract.

Two types of electrical potentials have been recorded. With the chloridized silver electrodes and the saline junctions, both in the stomach and on the forearm, a steady potential was recorded corresponding to what is commonly referred to as the D. C. potential. The rhythmic change, measured by all electrodes, is referred to as the A.C. potential. Both forms of potential vary markedly in different sites of the gastrointestinal tract. This variation led us to the development of multi-channel

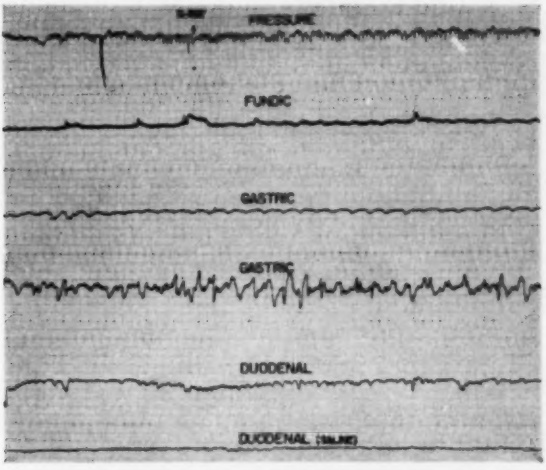

Fig. 2—Unit No. 134215 — Typical pattern recorded from an asymptomatic patient.

potential recorders for simultaneously measuring the electrical phenomena in different areas of the gastrointestinal tract. The normal gastric mucosa is always negative with respect to the skin. The A.C. potential of the upper portion of the stomach varies between 18 to 20 cycles per minute, whereas in the antrum it is 3 cycles per minute. The duodenum and jejunum exhibit a rate of 18 to 22 per minute.

Our present hypothesis is that the D.C. potential corresponds to mucosal activity. Experimentally this activity has been modified by anoxia and drugs that affect the vital functions of the mucosa. The A.C. potential seems to be related to the neuromuscular activity of the gastrointestinal tract.

Results. The subject group comprised 54 men and 11 women. The type of gastrectomy included 9 Polya, 13 Billroth I, and 43 Billroth II with and without vagectomy. These were performed 2 months to 21 years prior to the studies. In all, approximately 50 per cent or more of the stomach was removed.

The criteria for the diagnosis of the "dumping syndrome" have not been universally agreed upon. We have evolved a classification based upon those of Pulvertaft[3] and Saikku and Halonen[4].

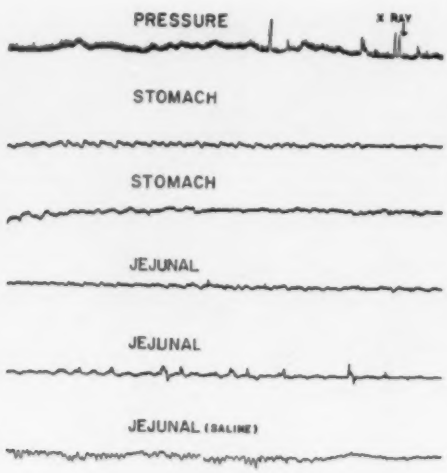

Fig. 3—Unit #721080. Postgastrectomy patient without symptoms. (Group 0)

We considered the following four groups:

Group O: Patients who made a rapid adjustment to a regular diet and have remained asymptomatic.

Group I: Patients who had minor dumping symptoms for more than one month or who had to forego certain foods to avoid distress. These patients have learned from experience the foods they must avoid and have adopted a certain discipline in living habits that allows them to lead a fairly normal life.

Group II: Patients with mild to moderate symptoms often relieved by lying down. Such symptoms have compelled the patients to make many adjustments in their ways of eating, resting after meals, or other changes in their activities to avoid or control the numerous symptoms.

Group III: Patients who have become incapacitated to the point of needing continuous care.

For purposes of orientation, a typical electrogastrographic curve obtained with electrodes at various points of the lesser curvature in an asymptomatic adult is shown in Figure 2. In patients who belong to group O the electrogastrographic pattern is similar to the above normal

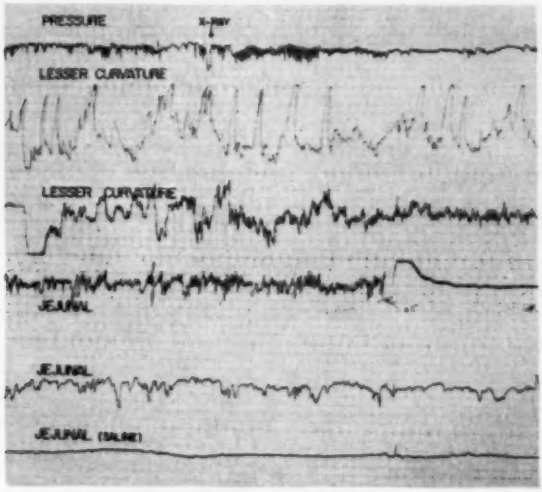

Fig. 4—Unit No. 777804 — Typical pattern recorded from a patient with dumping symptoms.

TABLE I—ELECTROGASTROGRAPHIC DIAGNOSIS

		0	*D+*	*D++*	*Total*
Clinical Diagnosis	0	51	1	0	52
	I	3	3	1	7
	II	0	0	4	4
	III	0	0	2	2
	Total	54	4	7	65

pattern (Figure 3). In patients with the dumping syndrome a markedly irregular electrical pattern is observed (Figure 4).

Table 1 summarizes the data on this group of patients. It can be seen that there is an adequate correlation between the clinical and electrogastrographic diagnoses of dumping. In both symptomatic and asymptomatic patients the electrical pattern was not influenced by the type of anastomosis or by vagectomy. Although the basic phenomena are not

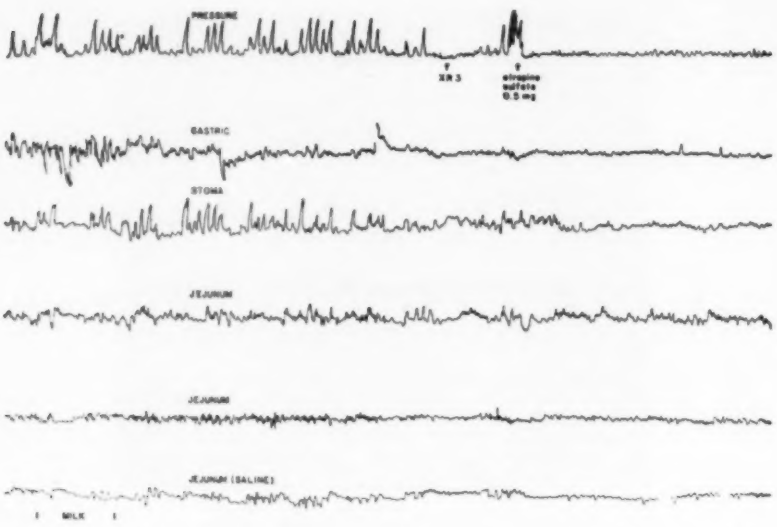

Fig. 5—Unit #269737. Patient A.S., with symptoms due to hyperactivity reflected in both the mechanical and electrical patterns. These manifestations subsided following the subcutaneous injection of 0.5 mg. atropine sulfate.

clearly understood, it appears that there is a local disturbance, either in the gastric pouch, in the intestine or in both.

Two patients will be described in order to point out the importance of combined studies in understanding the symptomatology of post-gastrectomy patients.

A.S., Unit No. 26-97-37, 66 year old female. A diagnosis of prepyloric and lesser curvature ulcers was made in April, 1956. In December, 1956, she underwent a subtotal gastrectomy (50 per cent) with gastroduodenostomy (Billroth I). In June, 1957, she complained of nausea and weakness after certain meals. In January, 1958, she experienced mild abdominal pain after ingestion of liquids but not after solid foods. These symptoms caused marked weakness. Electrogastrograms taken in January and in November, 1958, showed normal electrical patterns with mechanical hyperactivity. This disappeared soon after the subcutaneous injection of 0.5 mg. of atropine (Figure 5). These findings suggested that this was not a dumping syndrome but rather disturbed mechanical activity. Patient improved with anticholinergic drugs.

M.O., Unit No. 133-03-06. A 69 year old male with history of perforated

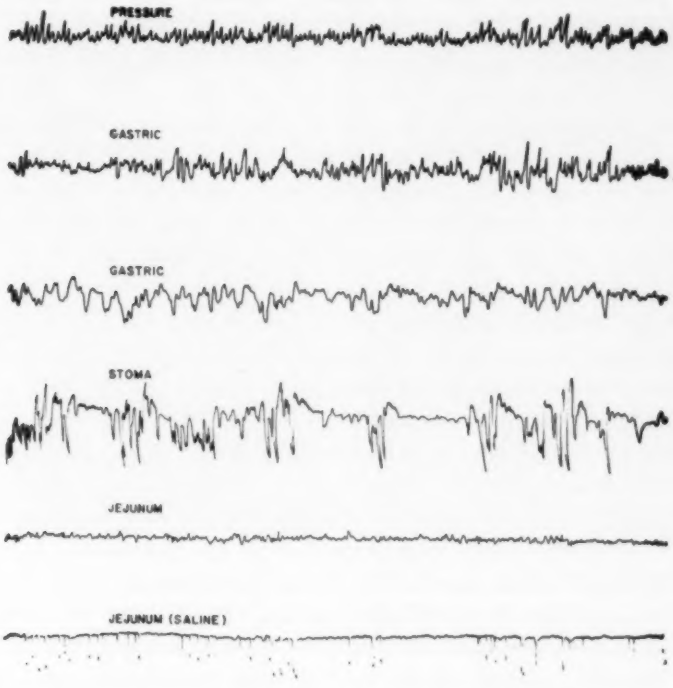

Fig. 6—Unit #1330306. Patient M.O. Electrical pattern suggestive of "dumping." No gastrointestinal symptoms but vasomotor manifestations of "dumping."

duodenal ulcer in 1932 and another perforated ulcer in 1952 while receiving steroids for rheumatoid arthritis. In July, 1957, a diagnosis of lesser curvature ulcer was made, which led to a subtotal gastrectomy with gastrojejunostomy (Billroth II). The patient has presented no further gastrointestinal symptoms but has complained of marked rhinorrhea after certain meals, relieved by lying down. These vasomotor phenomena were interpreted as an equivalent of "dumping". The electrogastrogram taken on November 12, 1958 showed irregular electrical patterns both in the jejunum and in the stomach (Figure 6).

Radiological Observations

The current investigation was planned primarily to provide physiological and morphological substrates in the radiological evaluation of

the postgastrectomy state. An equally impelling motive was the need for reappraisal of various concepts which have been contingent on roentgenographic and fluoroscopic observations made since Hertz's[5] original article appeared in 1913, and since Mix[6] evolved the concept of the "dumping stomach" in 1922. For the most part, these deductions have been based on examinations performed exclusively with a liquid barium suspension. To a lesser extent, other observations have had their origin in the apparent response of the upper gastrointestinal tract to a mixture of barium with a semiliquid meal compounded in a blender, or to a standard meal subjected to mastication by the patient. Accordingly, to obtain maximal information in the fasting state and also with food in the stomach, a composite examination was evolved. The initial phase employed a standardized non-flocculating barium suspension and was devoted entirely to a determination of the function and anatomical arrangements following gastrectomy. The second phase consisted once again of fluoroscopic and radiographic examination beginning almost immediately after the ingestion of a limited meal, such as a ham sandwich. All of the studies were performed by one radiologist employing a designated routine planned for the postgastrectomy state. This included evaluation of the gastric remnant, the mode of its emptying, the status of the stomach with respect to size and function, the anatomy and peristaltic activity of the small intestine immediately adjacent to the anastomotic site and the manner in which transit occurred through the intestine distally.

From the data obtained in examination of this series of patients, several observations appeared to be pertinent in establishing a frame of reference for a concept of normality in the postgastrectomy state, the range of variation within this group and the deviations suggesting abnormalcy. An outstanding feature was the similarity in the gross function of the gastric pouch and stoma, independent of the type of resection or anastomosis, in response to an inert liquid suspension. Consistently demonstrated was the fact that rapid emptying occurred as a physiological concomitant of the various postanastomotic structural arrangements when the range of variation in emptying of the intact stomach was used as a baseline. Even in the supine position with the effect of gravity at a minimum, a liquid bolus most often passed immediately and uninterruptedly through the esophagus, pouch and stoma into the adjacent small intestine. When the volume of ingested fluid

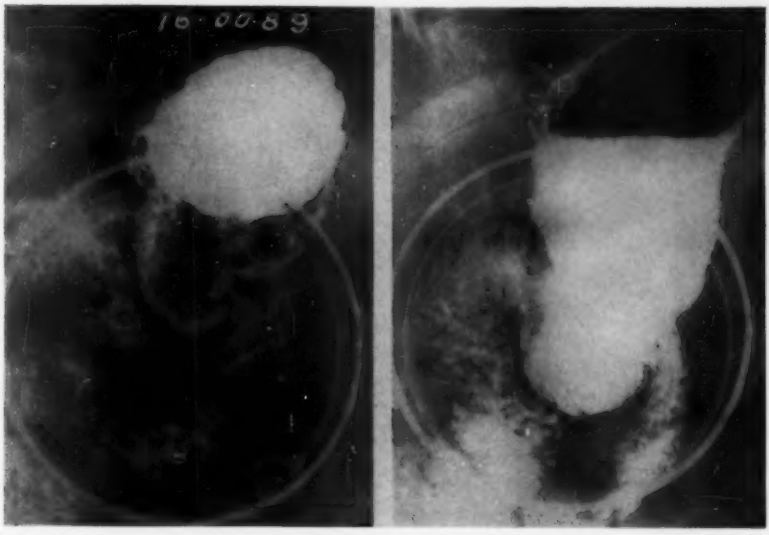

Fig. 7—Postresection and Polya anastomosis status, demonstrating wide gastrojejunal opening and jejunal pouch formation as well as the configuration of the afferent and efferent limbs. Reservoir capacity, in spite of the wide gastrojejunal stoma, was marked, with a large volume of barium. The patient is a 56 year old male who has been asymptomatic since surgery for duodenal ulcer five years earlier.

was increased, the gastric remnant functioned as a rapidly emptying passive conduit without intrinsic peristaltic activity or more than transient reservoir capacity. The latter seemed to be related inversely to the amount that the proximal small intestine would accept in a given period of time. Passage of a liquid medium in the presence of an artificial stoma was a rapid event which could not be quantitatively differentiated in terms of time, with the presence or absence of symptoms. Nevertheless, a range of variation was observed in pouch emptying and, specifically, an extremely rapid rate did not imply a symptomatic postgastrectomy state.

An even more realistic appraisal of pouch emptying and reservoir capacity was evolved by extended examination following the ingestion of a standard meal. A uniform response was the striking reservoir capacity for particulate matter, in spite of the previously demonstrated rapid emptying when an inert liquid was employed. This, too, rep-

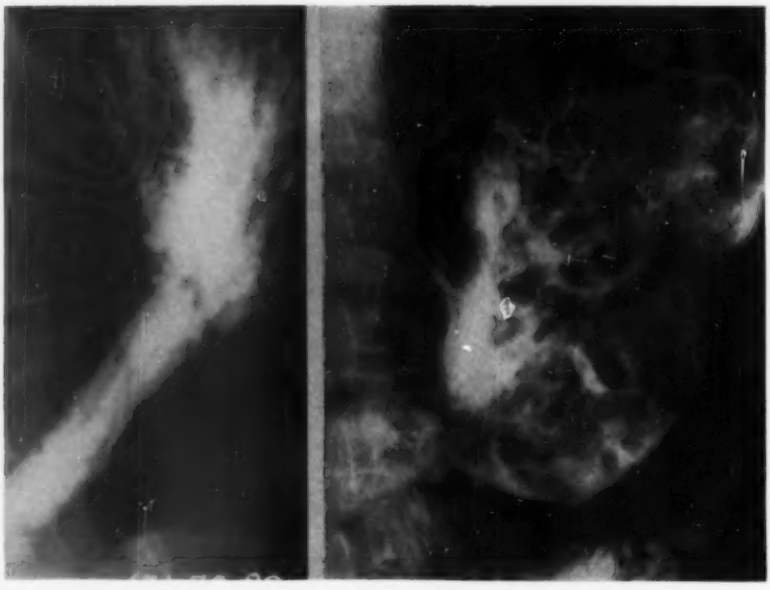

Fig. 8—Post-Billroth I status six months after surgery for chronic pyloric obstruction secondary to pyloric muscular hypertrophy. In spite of the marked reservoir capacity, as demonstrated with food, this 36 year old female's symptoms were clinically classified as the dumping syndrome. The rapid pouch emptying, with a liquid barium suspension, is similar to that noted in asymptomatic individuals.

resented a range of variation which bore no correlation with the type of anastomosis or status of the patient symptomatically. When a liquid barium suspension was administered in the presence of particulate matter in the pouch, selective rapid passage of the contrast material through the stoma was observed. In the course of emptying, particulate matter ultimately appeared in the small intestine after negotiating the stoma. Nevertheless, ingested food mixed with secretions and contrast material remained in the gastric reservoir for varying intervals, a period of one to two hours being relatively common.

In this group of patients, the stoma as such did not appear to have a determinative bearing on the function of the pouch and its emptying other than its role in obstruction when stenotic. After the initial phase of emptying, the width of the small intestine adjacent to the anastomosis determined, for the most part, the quantity of material accepted from

the stomach in a given period of time. This was apparent particularly in the Polya anastomosis, in which the wide gastrojejunal stoma played no role in gastric emptying. The effective exit stoma was governed by the efferent limb of jejunum and its width, and peristaltic activity determined the egress of material from the pouch. Such observations have been made by others[7]. Paradoxically, on the basis of the structurally wide Polya anastomosis, although functionally unrelated to emptying, various investigators have advocated reconstruction in an effort to correct postgastrectomy symptoms. Still others have directed their attention to the jejunal pouch opposite to the stoma as a factor in the production of symptoms in spite of this finding in patients with Polya anastomoses.

Gastric pouch size, as estimated at the time of surgery, did not appear to correlate well with radiographic documentation of size when a liquid barium suspension was used or when the stomach was distended with a semi-solid meal. The latter method has provided a more reliable index of pouch size, and surgically planned high resections have presented postoperatively large remnants which provided marked reservoir capacity for ingested food. Another morphological concomitant of the postgastrectomy state was the generalized prominence of the gastric rugae. This finding was almost universal and could not be related to the type of anastomosis or the presence of symptoms.

Following resection, and in the presence of an artificial stoma hardly resembling the pyloric mechanism in structure, various factors assumed importance in the mechanics of emptying. No gross peristaltic waves were observed in the gastric remnant unless, of course, the distal pars media was permitted to remain after limited resection. Such observations were made earlier by Groedel[8], fluoroscopically, and by Schindler[9], gastroscopically, who noted that peristalsis was not present proximal to the midportion of the body of the stomach. In a passive conduit, without propulsive waves, both the hydrostatic pressure of the ingested medium and extragastric forces such as gravity and respiration appeared to play major roles in emptying. With increase in intra-abdominal pressure, as in deep inspiration, coughing or sneezing, the diaphragm descended and the pouch size diminished, actively forcing material through the stoma. Of particular importance in expulsion of gastric contents into the small intestine was the effect of diaphragmatic motion[10].

When the stoma had been traversed, duodenal or jejunal peristalsis appeared to control the further transit of the contrast material or food distally; not infrequently, reverse peristalsis forced material in a retrograde fashion into the gastric remnant. The usual transit of material through the proximal small intestine was somewhat rapid, a phenomenon which generally was compensated for by prolongation in transit through the small intestine distally. Thus, the total transit time through the small intestine was hardly at variance with our concept of the range of normal, even with a consideration of the effect of food stimulation. In the ultimate evaluation of transit through the small intestine, there were no apparent differences which could be related to the type of surgery or the presence or absence of symptoms.

Certain conclusions appeared to be warranted based on the findings in this investigation of the postgastrectomy state. Although there were certain similarities in postgastrectomy function which were not a coefficient of the type of surgical procedure, there was a range of variation which precluded correlation with symptoms. This was particularly true when such factors as stomal size and gastric emptying were considered. Thus, in a patient with roentgenologically demonstrable rapid gastric emptying and what might be termed rapid transit through the small intestine, the deduction could not be made that the patient was symptomatic. Conversely, symptomatic patients did not show constantly the findings of an especially rapid rate of gastric emptying and diminished small intestinal transit time.

Conclusions

1. The findings in 65 patients who underwent subtotal gastrectomy for ulcer have been presented.

2. Patients with the so-called "dumping syndrome" exhibited irregular electrical activity not found in the asymptomatic patients.

3. By applying these diagnostic criteria, patients with the dumping syndrome were distinguished from other postgastrectomy patients.

4. Utilizing radiological methods of investigation, in which a wide range of variation in function was established in asymptomatic postgastrectomy patients, specific criteria for distinguishing the group of symptomatic individuals could not be established.

5. A diagnosis of "dumping syndrome" was not warranted from roentgenological findings in spite of the various techniques employed.

6. No correlation was observed between altered electrical activity by electrogastrography in patients classed as "dumpers" and the roentgenological findings.

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MANAGEMENT OF LOW BACK PAIN

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR MATHER CLEVELAND: Before we begin our discussion, I should like to call your attention briefly, by rough diagrams, to the development of the human spine from birth to its adult form. The newborn infant spine has a primary curve which extends dorsally, extending from the occiput to the coccyx. At the age of three to four months or up to six months, the infant first raises and then holds his head erect. At that time the infant develops a cervical lordosis. At 8 to 12 months of age the infant begins to stand. At that time he develops a lumbar lordosis. This is the essential structure of the adult spine with a cervical lordosis, posterior-dorsal, lumbar lordosis and posterior curve in the sacrococcygeal region. The dorsal and sacral spine, particularly the sacral area of the spine, are immobile, while the cervical and lumbar areas show great mobility. The points at which an immobile area of the spine joins a mobile area are subject to unusual stresses and therefore vulnerable to trauma. The cervical-dorsal junction, the dorsolumbar junction and the lumbosacral junction comprise these areas.

We are today considering the lumbosacral area, which is the most vulnerable and is most frequently the site of cause for complaint. Two cults of the healing art subsist largely on complaints arising in this part of the body. Thus, by the way of introduction to "my aching back", I now call on Dr. David Bosworth.

DR. DAVID M. BOSWORTH: When I was invited to discuss orthopedic conditions as a cause of low back pain and their treatment, I was reminded of the man who mounted the scaffold and was greeted by the hangman with the question as to whether he wanted to say something and he said, "Yes, I have a lot to say but I doubt if there is going to be time enough in which to say it."

The subject of low back pain and disability is such a broad one that no one person can cover it as it affects one field of medicine, much less one segment of the problem, in ten minutes.

To begin with I want to dispel a few myths regarding low back pain. First, low back pain is not always due to low back pathology. It is a myth that it is. It may be due to widespread pathology and to various causes. Secondly, the sacro-iliac joint is rarely, if ever, a cause of the so-called sacro-iliac syndrome, sacro-iliac pain. The sacro-iliac joint is practically an asymptomatic joint as far as pathology is concerned. I have seen it totally destroyed by tumor and totally destroyed with infection with minimal symptomatology. The so-called "sacro-iliac

strain" is practically always related to lesions of the lumbosacral spine and not to the sacro-iliac joint.

Where surgery is indicated in the treatment of low back pathology a competent surgeon is the one to do the operation but certainly not a team of surgeons with divergent ideas and divergent attitudes. Either a neurosurgeon or an orthopedic surgeon should be chosen, depending upon the indications, but certainly a team of two surgeons is not required and such an arrangement can sometimes be a great disadvantage.

Where lumbosacral pathology is present, as in the case of a lumbar herniated or lacerated disc, removal of the pressure on the nerve roots with relief of the neurological signs and symptoms does not reconstruct that back. The patient has lost his supporting disc and is still comparable to running on a flat tire. He needs fusion and fusion should be done at the time of removal of the disc. I care not whether an orthopedic surgeon or a neurosurgeon does such fixation. Many neurosurgeons are now doing primary fusions in the lumbar area and I am glad of that.

Another myth is that the obtaining of myelograms involves an innocuous procedure. It does not. It is a tricky thing to do. It may cause arachnoiditis on occasion, and symptomatology therefrom may be as great or greater than the symptoms and disability caused by the original herniated disc. Furthermore, on the occasions in which such an arachnoiditis occurs, the patient has literally to be born again if he is ever to recover from his arachnoiditis. Myelograms should be reserved for those cases in which tumor or pathology other than a herniated disc is suspected. In my opinion it is wiser to explore where a definite diagnosis of herniated disc is made, even with the chance of missing on the diagnosis. Re-exploration can be done and it is better to accept this than to do a myelogram initially. Also, myelograms may fail to show true pathology in many instances and at other times may suggest pathology that is not actually present.

Another myth is that a correct diagnosis can always be made as to the cause of lumbosacral pain, either preoperatively or with certainty postoperatively, in nearly 100 per cent of cases. In my experience this is not so. There are many cases in which we never discover the real cause of lumbosacral pain.

From an orthopedic point of view the causes of lumbosacral pain can be grouped in various areas. First, is that of strain, strain indicating actual tearing, whether in very small areas or in large areas of ligamentous

structures. These cases are treated simply and usually recover satisfactorily with strapping, brace, belt, heat, fracture board on the bed, avoidance of unusual activities for a time and other simple measures. A second group is that of fractures. In my experience fractures involving the bodies of the vertebrae which are not too extensive are best treated conservatively and if they do not show neurological manifestations, recover quite readily and in the great majority of instances without surgical intervention.

The next group includes congenital defects and abnormalities in the lumbosacral spine. These conditions are usually not the cause of the pain of which the patient complains. However, they are evident on x-ray films. The abnormality occasionally seen is the half or hemivertebra. Actually, they rarely cause disability or back pain and are better left alone and the cause of the back pain sought elsewhere.

Next is the developmental group of lesions such as scoliosis. Where curvature of the spine or scoliosis is extreme, stress and strain applied to the spine may cause pain. Such cases need evaluation by those specially equipped to handle and investigate these conditions and usually do require surgical measures, not just conservative management.

Another class of cases includes neoplasms of the spine. Neoplasms involving the vertebral column, especially if metastatic, may be extensive and no measures may be available for reconstruction or relief. In some instances, however, the neoplastic involvement is so localized that collapse of the local area can be prevented by arthrodesis until satisfactory control can be gained by roentgen irradiation. Spinal fusion may be indicated here and is not only permissible but is actually very valuable in preventing the collapse which may occur and thereby prevent neurological manifestations, pain or paralysis.

Infections are another group of lesions involving the lumbosacral area and the rest of the spine. Tuberculous infections and those caused by other organisms are common. These, of course, should be treated for the specific infection present and that implies proper diagnosis before treatment. Thorough investigation may require needle biopsy. Where involvement is extensive, the necessity for fusion support may and probably will be indicated even though the infection may be controlled. We can now control most tuberculous infections but fusion is necessary to prevent the spine deformities resulting from the defects caused by the infection.

The effects of metabolic disorders are also seen by the orthopedic surgeon, particularly senile atrophy of bone, with multiple compression fractures, gradually increasing in extent and number of vertebral segments involved. Such bone lesions resulting from metabolic disorders are best treated conservatively with testosterone and with high protein intake, bracing, corset support, bed rest and other similar measures.

There is one outstanding example of a lesion which produces symptoms closely simulating those of the herniated disc or extradural pressure therefrom. That condition is spondylolisthesis with failure of union of the arch of the vertebra, usually in the lower lumbar region. This failure of union of the arch permits slippage forward of the spinal column above on the segments or sacrum below. Such lesions, once pain is initiated, require fixation since pain will almost certainly be recurrent and increasing in amount, together with attendant disability. It is a fairly common condition. Perhaps two or three out of every 100 patients will have this condition but without symptoms for many years. As ligamentous support structures become more rigid and less resilient, a slight strain may cause onset of symptoms. From that time on, the fat is in the fire, so to speak, and reconstruction is essential.

In my practice I have a good many cases referred to me for fusion after they have had prolonged conservative care. Nevertheless, I operate on about only one out of four cases; in other words, three-quarters of the patients referred for operation are satisfactorily managed without surgery even though many of them present definite, obvious defects that might legitimately be thought to require operation.

(Slide) Here is a long list of incorrectly diagnosed conditions in which the symptoms closely simulated those associated with a herniated disc which was the real cause of the pathology.

(Slide) You will recall that I said we cannot nearly approach 100 per cent correct diagnosis, even after operating on the patient. This slide is an outline only and yet on that outline are 25 or 30 figures representing different classes of lesions which can and do closely simulate extradural pressure caused by a herniated disc. This slide does not list all of the lesions which can produce symptoms and signs similar to those caused by a herniated disc but it does indicate the broad spectrum or broad field of pathology which makes the diagnosis of disc herniation difficult. Being aware of how common herniated discs are, it would perhaps be better for the present to suspect that each patient who com-

plains of low back pain and possibly of sciatica also, may possibly have a herniated disc and then proceed to try to prove that he has not.

(Slide) To make an accurate diagnosis requires a careful evaluation of each case and this cannot be done on a large number of patients on any one day. One must take time and adhere to a first principle, learned in medical school, to obtain a complete and accurate history. This would include an account of the mode of onset, a history of possible injury, whether the attacks have been single or multiple, the location, shift and radiation of pain areas and whether these match known anatomical pathways. A careful and thorough examination is also essential. This would include not only the positive objective findings, but measurements, reflexes, testing of sensation and rectal and gynecological examinations as well. If abnormal neurological findings are noted a neurological consultation is desirable at this time. Finally, with roentgenograms showing the defects that occur in the lumbar area, narrowing and immobilization of intervertebral discs and local hypertrophic changes, one can arrive at a fairly accurate diagnosis regarding the presence of a herniated disc or the presence of some other pathology causing similar symptomatology.

MODERATOR CLEVELAND: I will now call on Dr. Bronson Ray.

DR. BRONSON S. RAY: A neurosurgeon's interest in low back pain has to do with those conditions which produce some involvement of the nerve roots of the cauda equina in addition to back pain. The conditions in question are principally neoplasms and alterations in the intervertebral discs. The term "alterations" of the intervertebral discs is used advisedly because there is a variety of pathologic changes in the discs which are not accurately designated by the many synonyms rather loosely employed such as ruptured disc, slipped disc, herniated nucleus pulposus, lacerated disc or annulus fibrosis, hidden disc, degenerated disc, spondylosis, etc.

Sciatica is a syndrome that is the clinical manifestation of compression-irritation of a nerve root, usually by an abnormality of the disc. The term "sciatica" means pain in the lower limb; it is not synonymous with sciatic neuritis. And strictly speaking, the condition is one of radiculitis, i.e., irritation of one of several roots which give origin to the sciatic nerve.

Pain limited to the lower back is probably not the result of the radiculitis, but initially comes from distention of the annulus fibrosis

by the bulging nucleus pulposus. It is a common occurrence that, as the annulus ruptures or tears completely to allow extrusion of the nucleus pulposus, the tension on the annulus ceases and the backache ceases, but simultaneously the nerve root is compressed by the herniated fragment of nucleus pulposus. But the important point to emphasize is that this sequence illustrates that, for a time, back pain alone may be the manifestation of the incompletely ruptured disc. This kind of back pain may recur in acute attacks, often referred to variously as lumbago, sacro-iliac strain, lumbosacral strain, etc.

The sciatic syndrome incorporates a number of symptoms and physical signs, not all of which are present in every patient. But if one were to reduce the clinical picture to one symptom and one sign they would be radiating pain in the posterolateral aspect of one lower extremity from buttock to ankle and painful limitation of flexion of the thigh with leg extended at the knee, on the side of the pain. Associated paresthesias, numbness, muscular weakness and wasting, and reflex changes are variable in their occurrence.

The diagnosis is relatively simple and certain for typical cases, which are in the majority. Atypical symptoms and signs introduce the possibility of other diseases, the most important of which are neoplasms. Metastatic tumors of the vertebrae are fairly common, particularly in cancer arising in lung, prostate or breast. The common types of primary tumors of the region are chordomas (extradural) and intradural neurofibromas, meningiomas or ependymomas.

Briefly, it can be said that tumors can be expected to produce progressive and unremitting pain (contrasted with the pain caused by a ruptured disc) and tumors are much more likely to cause bilateral symptoms and signs.

Roentgenograms of the lumbosacral spine are always worth having, for whatever can be learned, though in the case of a ruptured disc one doesn't learn much. If one does see a significant narrowing of one of the intervertebral spaces it is more than likely not to be the offending one.

A lumbar puncture is of little value in the case of a ruptured disc and not more than half show an elevation when the total protein of the spinal fluid is determined. For differentiating a tumor, however, the lumbar puncture is important; rarely does a ruptured disc cause an elevated protein content over 100 mg. per cent, whereas a tumor

usually causes a protein content over 100 mg. per cent.

Myelography in my opinion is in about the same category of usefulness as the spinal fluid examination. One usually does not require a myelogram to make the diagnosis, to determine the level or to decide about the need for operation in a case of ruptured disc and there are a few disadvantages to the procedure. But for differentiating ruptured disc and tumor, myelography is invaluable.

The indications for operation in the case of a ruptured disc are: 1) continued disabling pain after an initial period of non-surgical ("conservative") treatment; 2) the development of palsies, the commonest of which are in dorsal or plantar flexion of the foot; and 3) neurogenic impairment of bladder control.

It is the first of these indications which gives rise to such variable interpretation and opinion: How much pain is disabling; how long should the patient try non-surgical treatment; and what constitutes appropriate, intelligent non-surgical treatment, and a most disturbing additional question, how much chance is there for irreversible symptoms and signs to occur if the condition goes on month after month?

Certainly any dogmatic attitude about the management of a ruptured disc is in error. To insist that all patients require an operation or that the operation has no place in the treatment is equally indefensible. Many patients who refuse or are denied operation miss an opportunity for reasonably quick and permanent relief of their symptoms. On the other hand, operation does not always give the complete and speedy relief that is hoped for.

There is no doubt that many recover from ruptured discs spontaneously and, fortunately, this often takes place within the first several weeks, up to 6 or 8 weeks. Spontaneous recovery from symptoms occurs as a result of shrinkage and beginning absorption of the nucleus pulposus. This has guided my own thinking and practice with regard to surgical treatment. As I see it simply, if nature does not remove the offending nucleus pulposus, the operation is designed to do it instead by merely lifting out the nucleus pulposus, which has already lost its right of domain anyhow.

The need for fusion of the vertebral joints, I feel, should be a highly individualized matter and I do not recommend or employ it for patients who have a straightforward syndrome of nerve root compression of not too long standing. Some small percentage of patients who

fall in this group may subsequently require spine fusion, but I believe the number would not exceed 5 or 10 per cent in the group I have in mind. In other patients with long histories of predominant back pain and minimal radiculitis–some of whom might have profited by early removal of the nucleus pulposus–decompression of the nerve root combined with spine fusion may be more appropriate.

Unfortunately, I do not have an up-to-date follow-up of my series, though I can refer to a study made several years ago.

A colleague reviewed results in about 350 patients I had operated on in a five year period, the review being made five years after that. He chose his own criteria without influence from me and he reported as follows:

Excellent, absolutely free of pain or other symptoms referable to the back in unrestricted activity–18 per cent.

Good, satisfied with the result and uncomplaining and doing their regular work, though occasionally subject to some symptom believed to be related–60 per cent.

Fair, relatively more complaints than those classified as "good" but able to work at same or lighter occupation–15 per cent.

Poor, dissatisfied with result of operation, though some doing limited work and none made worse by operation–7 per cent.

But statistics are impersonal and people with backaches can get very "personal". No doctor continues to use a form of treatment which leaves his patients dissatisfied; not only would his life be made unhappy, but he would be likely to go out of business. From the standpoint of my experience with a large percentage of satisfied patients, I see no reason to alter the opinions regarding treatment I have just listed.

MODERATOR CLEVELAND: Thank you very much, Dr. Ray. I will now call on Dr. Albert H. Aldridge.

DR. ALBERT H. ALDRIDGE: Low back pain is a complaint of 80 to 90 per cent of the female patients who come under treatment for abnormalities of their pelvic organs. Reliable studies have shown that backache is, in part or entirely, gynecologic in origin in 40 to 50 per cent of these patients. An experienced gynecologist is aware of the variety of etiological factors which may be responsible for low back pain. He must be cautious always in deciding whether the backache of which any woman complains is caused by the pelvic abnormalities which he finds on examination, or whether it is due to one of the many conditions

to be discussed by other members of this panel.

Gynecologic backache is usually low and in the midline, that is, in the sacral or lumbosacral region of the back. Authorities are not agreed as to the exact nature of tissue changes and reactions which are responsible for this type of back pain. It has been attributed to various factors which include: 1) Pelvic congestion; 2) Tension on ligamentous and fascial supporting structures of the pelvic organs; 3) Pelvic pressure from retroverted uterus, uterine or ovarian tumors or ovarian cysts; 4) Distention of, or traction on, the pelvic peritoneum; 5) Involvement of pelvic nerves by extensions or metastases from malignant tumors of the pelvic organs.

Pelvic congestion may be physiologic or pathologic. It is a common cause of: 1) Low back pain, before and during menstruation, in women who have normal pelvic organs; 2) Low back pain due to various abnormalities of the pelvic organs; 3) Aggravation of an existing gynecologic backache during menstruation.

The uterus is supported at a normal level in the pelvis by the musculofascial structures of the so-called upper pelvic floor. Uterine prolapse occurs when these supporting tissues are damaged or become relaxed, usually as a result of childbirth. Congenitally poor development of these same structures predisposes to uterine prolapse in some women and is responsible for the prolapse occasionally seen in a nulliparous woman.

Women who have uterine prolapse frequently complain of a bearing down sensation in the pelvis, and of sacral or lumbosacral backache, believed to be due to tension on the ligaments and fascial structures which support the female sex organs. Surgical procedures to correct uterine prolapse may fail to relieve its symptoms, including backache, until the functional integrity of the upper pelvic floor is restored by suitable plastic procedures. Uterine prolapse is likely to develop near or past the menopause. It usually occurs at a time of life when many women suffer from other physical abnormalities such as obesity, arthritis and various orthopedic conditions. Combined gynecologic and orthopedic abnormalities are not infrequently responsible for their low back pain.

It is a well known fact that 20 per cent of women are born with the uterus in a retroverted position. In many women this misplacement is asymptomatic and may be regarded as a variation of normal for as

long as it fails to produce symptoms. Eventually, conditions associated with retroversion may cause functional disturbances of the pelvic organs and various symptoms, including a bearing down sensation in the pelvis and low back pain. In contrast to some orthopedic backaches which improve with physical activity after getting up in the morning, a backache from retroversion is likely to occur, or to cause more discomfort, at the end of the day when a woman is physically tired. The exact cause of low back pain in women who have an uncomplicated retroversion is not known. It has been attributed to pressure from the misplaced uterus, pelvic congestion, and to abnormalities of the uterine supporting structures which have allowed the retroversion to occur. Retroversion is not uncommon in women who have pelvic inflammation or endometriosis. In these circumstances, low back pain may be due in part, or entirely, to adnexal disease rather than to the misplaced uterus.

In some women backache from an uncomplicated retroversion can be completely relieved by holding the uterus in normal position with a pessary. This diagnostic test cannot be used if the uterus cannot be replaced, or if it cannot be held in normal position with a pessary. In such circumstances or when there is doubt as to the cause of the backache, the patient should have careful diagnostic studies. If no other cause for the backache can be found, an operation for retroversion is, as a rule, justifiable and is likely to be followed by a satisfactory result. In the past, many operations to relieve backache, presumed to be due to retroversion, have led to disappointing results.

For the purpose of this discussion, benign tumors of the uterus and ovaries, and ovarian cysts, may be considered as a single group of conditions which may at times cause low back pain. Whether or not they do so depends largely upon their size and location. If they are located in the true pelvis and are large enough to produce pressure they may cause many symptoms, including low back pain. Discomfort from pelvic tumors and cysts is likely to be more severe if they develop in the broad ligaments or in the retroperitoneal space and when they are accompanied by adnexal disease, that is, pelvic inflammation or endometriosis. Malignant pelvic tumors rarely cause low back pain until they extend or metastasize to structures along the lateral pelvic walls including the pelvic nerves, or until they metastasize to the bones of the pelvis or to the lumbar vertebrae.

It is known that distention of, or traction on, the peritoneum will

cause pain. This may occur in the pelvis from torsion of the uterus or of the pedicles of ovarian tumors or cysts. These abnormalities may also cause low back pain.

It is believed that low back pain in gynecologic patients can be caused by muscle spasm which occurs, at times, as a protective reaction to irritation of the peritoneum of the pelvis. The common irritants responsible for this reaction include: chemicals injected into the uterus to induce abortion, or opaque materials used for uterosalpingograms; exudates from ruptured pelvic tumors or cysts; purulent material from adnexal infections; blood from extrauterine pregnancy or rupture of a corpus luteum; and endometriosis.

Some gynecological patients who have low back pain and other symptoms come under treatment for large uterine tumors, ovarian cysts, adnexal disease, endometriosis, or extensive birth injuries. They have clear-cut indications for surgical operations. For these women, surgeons are justified in carrying out whatever treatment seems necessary. Diagnostic studies and suitable treatment for persistent postoperative backache can be carried out later.

A difficult problem arises at times when a woman has low backache as her predominant complaint and an abnormality of her pelvic organs, such as a retroverted uterus which may or may not cause backache and which does not urgently require surgical treatment. It is in such circumstances that diagnostic studies are important to determine whether the backache is gynecologic, orthopedic, urologic, neurologic or psychogenic in origin. It is not unusual for a woman to have more than one cause for her backache. For example, it may be due to a combination of orthopedic and gynecologic abnormalities. It is also known that the cause of low back pain in many women, who have definite abnormalities of their pelvic organs, is entirely orthopedic rather than gynecologic in origin.

There can be no doubt that disturbing symptoms referable to the pelvic organs can originate from, or be exaggerated by, subnormal physical health and emotional frustrations. They are not uncommon in women who suffer from emotional insecurity, unsatisfactory adjustments to marriage, the fear of having an unwanted pregnancy, cancer-phobia and so forth. The possible effects of these nervous problems on a woman's gynecologic complaints may be obvious as soon as she comes under treatment, or they may become apparent only after

continued observation and unsatisfactory response to treatment. Physical examination may reveal no cause for the low back pain of which some of these women complain.

For proper management of abnormalities or diseases of the pelvic organs in any woman, the gynecologist must take into consideration her age, her marriage status and the importance of preserving her menstrual and childbearing functions.

MODERATOR CLEVELAND: Now as an indication that mind is often master over matter, we call next on Dr. Samuel F. Thomas.

DR. SAMUEL F. THOMAS: It has been said that while there is life there is hope. For us in psychiatry, while there is talk there is hope. We try to keep the patient talking.

I should like to discuss first, the back in the body image; and second, the distinction between various syndromes.

The back in the body image and in the language of the body image is an area in which strength and energy reside, and upon which troubles are piled: back-breaking work; carrying dependent relatives on one's back; the last straw; back-bone; flat on my back; get my back up. It is connected with the reproductive organs: the back affects the potency; the womb affects the back. The spine is even more vital. If someone has mentioned the spine, the patient will often be especially impressed; there is now a definite medical entity like a sluggish liver, or a virus, or the glands. Further, a crooked spine must be weak; and people notice it.

It will be important to observe what kind of process is at work.

1. The neurasthenic group: The leading symptoms are fatigue and weakness. The very concepts of fatigue and weakness dominate the symptoms. If you are tired, your eyes are tired, your back is tired. "Always had a weak back." Incipient depression may be masked under this complaint-system.

2. The hysterical group: Complaints and disabilities in the general domain of the somatic nervous system; not in conformity with its known anatomical lines but in accordance rather with popular, obvious, commonplace subdivisions of the body image: The arm, the leg, the back, the whole side. Symptoms often develop by a reference resembling or identical with ordinary suggestion. Characteristically, there is a history of various previous symptom flurries of a similar kind; and usually a conception of immediate trauma. We are often able to discover

a double-layer of motivation: an obvious, superficial one, for instance, a bid for avoiding work; a deeper one involving trends of passivity and hostility; attitudes covering retaliation toward the self and others; and so on.

3. The hypochondriacal group is different. Here we have nearly delusional concern and preoccupation with organs, bodily function, and diseases, organized around the patient's own special body image, which in itself is often built up along bizarre, autistic lines. There is an attitude of eagerness, almost of gloating. The psychology of hypochondriasis is obscure. A hypochondriacal phase may be seen as a sort of partial recovery stage from various severe breaks; as an ominous precursor of the schizophrenic psychosis, or again as a chronic fixed attitudinal disorder of the personality.

4. The psychosomatic group: Here, broadly speaking, we have a demonstrable physical change brought about by the physical processes underlying the emotions. The processes are generally mediated by the autonomic nervous system. A concept of psychogenic muscular tension is often invoked; but I am not convinced that many backaches belong to this particular mechanism. The hysterical and neurasthenic groups are in my experience the commonest background for psychogenic factors in backache.

Certain physical signs may give a preliminary hint as to the presence of emotional "overlay": disproportionate tenderness to palpation, with skin tenderness; equal tenderness of spines and both paraspinal muscular masses; upward radiation of pain; lack of relief by ordinary measures; vigorous writhing motions. Note, however, that odd camptocormic postures (as opposed to movements) are not reliable indications. These camptocormic postures may represent the guarding contraction in an organic case.

Finally, we have anomalous response to the Lasègue maneuvers. However, the whole psychiatric history and status are the only ultimate sources for conclusions. Management of a severe case, for example, with severe pain, severe limitation, constant complaining, disputed physical findings, history of polysurgery, addiction—management of such a case requires a great deal:

1) Setting aside of the superficial motivations so far as possible. It is difficult to treat a patient in the midst of a hugger-mugger overliability.
2) The highly prevalent passivity trends should be taken into account.

The patient must have protection and solicitude. 3) The backache should not be blamed point blank on motives. These factors should be developed independently of the complaint in the guidance-interview. 4) Finally, even the mildest addiction problems are best handled on an in-patient basis, a closed service, if need be, without faltering. Ambulatory insulin and methadon step-down sometimes give superb results. A very gradual technique is desirable. Placebo action of medicines at a minimum. The patient should not be deprived of satisfaction in the effort to wean himself from the drug. It may be noted that the normal, healthy reaction to a placebo is temporary improvement. There is a leeway of suggestibility in most of us. The true hysteric holds out with his pain right down to general anesthesia, even with drugs which would alleviate a case of osseous carcinoma.

MODERATOR CLEVELAND: We have a number of questions and I shall submit them to the various members of the panel to whom I think they may be appropriate.

I ask Dr. Aldridge the following question: On what basis is operation for uncomplicated retroversion of the uterus justifiable for relief of low back pain and, following that, in what percentage of women is operation successful in relieving low back pain due to uncomplicated retroversion of the uterus?

DR. ALDRIDGE: Management of uterine retroversion has changed drastically in the past 25 to 30 years. Present day treatment of this condition is based on the fact that 20 per cent of women have congenital retrodisplacements of the uterus and that many are asymptomatic throughout life. In a few women, retroversion, and conditions associated with it, cause symptoms which can be relieved by surgical correction of the misplacement.

Indications for an operation for retroversion may develop at any time from the late teenage years to the menopause. Rarely is operation indicated solely for low back-pain due to retroversion. Most of these women have one or more gynecological complaints which include pelvic pain, menstrual disorders, dyspareunia, pelvic tenesmus, sterility and so forth. Such symptoms may occur in women who have uncomplicated retroversions.

Operation for retroversion is never an urgent surgical procedure and for this reason there is always time to carry out diagnostic studies to determine the cause for pelvic symptoms in a woman who has a

misplaced uterus. There is probably no better test to establish a proper indication for operation for retroversion than to hold a misplaced uterus in normal position with a well fitted pessary for two or three months. If this procedure is followed by relief of pelvic symptoms, including low back pain, a satisfactory result from operation can be expected. If the uterus cannot be replaced or cannot be held in normal position with a pessary, careful studies should be made to rule out the causes for low back pain which have been discussed by other members of this panel. If no other causes for the low back pain can be found, an operation for retroversion is likely to produce satisfactory results.

The results of excellent clinical studies to determine success of operations for retroversion have been made and published by the late Dr. Frank Lynch, at the University of California, and by Dr. Edward A. Bullard and the late Dr. George Gray Ward, at the Woman's Hospital. The outcome of these studies was approximately the same and showed that four out of five women who are properly selected for operations for retroversion get relief from their pelvic symptoms including low back pain.

MODERATOR CLEVELAND: *I have two questions that I shall direct to Dr. Bosworth. They are relatively short: Are there cases in which roentgenograms with the patient in the standing position are of value in diagnosing the cause of low back pain? That is the first, and the second is: What is the management of herniated fat pads in the lumbospinal muscles?*

DR. BOSWORTH: I don't know that there is any particular advantage in having roentgenograms taken with the patient vertical. On theoretical grounds one might expect that a lacerated disc would show its greatest narrowing when the weight of the patient's upper extremities and trunk were superimposed upon the disc. But actually, I have not taken roentgenograms in that position recently. We tried that many years ago but had results of no particular diagnostic value.

The other question, as to the cause of symptoms from tender fat pads or lipomas located in the lumbar region, is a condition in which the symptoms are not particularly distressing and they are readily evaluated. In my experience they have not been confusing and have usually been associated more with the field of Dr. Thomas in neuropsychiatry than they have in that of structural orthopedics.

MODERATOR CLEVELAND: That question was also addressed to your

Moderator and I would like to say that I have rarely, if ever, seen a fat pad that I thought was the cause of backache, nor have I ever seen a patient's symptoms relieved by the removal of a fat pad.

Dr. Ray, this is not a question, this is a statement, but I would like you to comment on it. This physician states: "From my own experience, most low back pains have no definite pathology. Most low back pains improve almost instantly with injections of procaine into the region of the pain. Very often there is no return of pain for a very long time and at times improvement is permanent."

DR. RAY: I am not sure whether I am supposed to refute that or to endorse it, but my reaction would be that there certainly are pains in the lower back which result largely from muscle contraction. This may be the result of poor posture or it may be the result of tension states, or indeed sore muscles may add to the painful state from a number of etiological factors. If injecting procaine is helpful it would seem to me the benefit would have to be based on a temporary relaxation of muscle contractions in that region. I believe it takes a good stretch of the imagination, though, to conceive of any important disease that would be cured by an injection of procaine. I personally avoid the injection of procaine because I find I could soon become absorbed in that kind of effort and have little time left for other things that I think I can do to advantage. I might add that I have not been impressed with any beneficial effects from injections of procaine or other anesthetizing agents in cases of frank sciatica due to herniated nucleus pulposus, unless it be for some partial relief of the painful muscles. Occasionally I have seen unhappy results when needles have been put directly into the sciatic nerve. This may give rise to a most disturbing problem since the patient then has not only radiculitis but in addition has a true sciatic neuritis.

MODERATOR CLEVELAND: In your answer you have also answered the query of another doctor, who asks the opinion of the panel on the use of local anesthetics in the treatment of herniated discs.

Dr. Bosworth, I would like to ask you, what use has traction in the treatment of herniated intervertebral discs?

DR. BOSWORTH: I think the value of traction *per se* in the treatment of herniated intervertebral discs is another delusion. If the patient is to have traction he is put to bed. Most patients with extradural nerve root pressure are more comfortable when lying down than they are when

standing and with several days' rest in bed will be relieved with so-called traction. I think it is a little difficult to conceive of traction influencing the disc since one applies the traction to the legs without any appreciable counter-traction on the trunk above. It is more or less as though the traction is exerted against a fixed point. I know that patients who have traction applied are relieved but I think that is mainly due to the bed rest and immobilization.

MODERATOR CLEVELAND: *I should like to ask Dr. Thomas if both psychogenic and anatomic causes of low back pain may be present in the same patient? If they are, to which should the physician give priority in treatment?*

DR. THOMAS: Both are frequently present, in fact almost invariably, and I cannot decide the question of priority. I like to work concurrently with the organicists on the patient's disorder.

MODERATOR CLEVELAND: *Dr. Aldridge, how would you treat a woman who developed severe pelvic and low back pain due to retroversion when she is three and one-half months pregnant?*

DR. ALDRIDGE: Severe pelvic and low back pain in a woman who has a three and one-half month pregnancy and a retroverted uterus are usually due to pressure from incarceration of the uterus in the hollow of the sacrum. Relief of symptoms is usually dramatic following dislodgment of the uterus from its fixed position. As a rule this can be readily accomplished by placing the patient in a lithotomy or knee-chest position and exerting gentle upward pressure on the fundus of the uterus. Patients who are uncooperative or too sensitive should be anesthetized before efforts are made to replace the uterus. At times it is easier to dislodge an incarcerated uterus by digital pressure through the rectum. This permits pressure on the upper surface of the uterus at a higher level than by the vaginal route.

A pregnant uterus which is large enough to become incarcerated will invariably stay in normal position after it has been dislodged. For this reason, a retroversion pessary to prevent recurrence of the incarceration is, as a rule, unnecessary.

MODERATOR CLEVELAND: *Here is a question that has just come up. What percentage of patients with low back pain do gynecologists send to orthopedic surgeons—or to neurosurgeons and psychiatrists also?*

DR. ALDRIDGE: I am sure there are no data to indicate the percentage of patients referred by gynecologists for orthopedic, neurologic and

psychiatric consultations. There can be no doubt that such opinions are being sought much more frequently than in the past.

Gynecologists are now well aware of the many emotional and physical conditions which may cause or aggravate symptoms which patients believe are due to abnormalities of their pelvic organs. Careful postoperative follow-up records have done much to convince gynecologists that many surgical failures can be avoided by careful preoperative diagnostic studies, including the opinions of experts in other fields of the practice of medicine.

MODERATOR CLEVELAND: *Here is a question for Dr. Ray: Do you feel that electromyographic studies are helpful in determining the cause of low back pain? If so, when and how?*

DR. RAY: Well, I should like to answer charitably about that but must say that personally I have not employed electromyography very often for this problem. But there are those who have, and who, with their skill and interest, are able to determine a good deal about whether a nerve root is involved, to what degree it is involved, whether more than one nerve root, and so on. I find, though, that one's clinical judgment, for all practical purposes, accomplishes just about as much.

MODERATOR CLEVELAND: *We have two questions relating to manipulation of the back for low back pain, whether it is done by the physician or by the osteopath, or by other cultists, and how effective it is in the relief of low back pain. I personally think manipulation helps at times but unless the operator has first seen a roentgenogram of the region, I believe it is unwise to manipulate a spine. I shall ask Dr. Bosworth to comment further on that.*

DR. BOSWORTH: I know that manipulation will frequently give considerable relief to the patient and I know the methods of manipulation that are commonly used. On the other hand, I have seen instances in which manipulation, done even after a complete study and with realization that the lesion basically was probably extradural pressure from a lacerated or herniated disc, has converted the lesion from a simple one into a more complicated one. I myself never manipulate a spine for low back pain. Patients who have such manipulations done with relief invariably have a recurrence of symptoms at a later date. I advise the patient of the possible dangers. The patient as a free agent, may choose another physician to manipulate his spine if he so desires.

MODERATOR CLEVELAND: *I have another question for Dr. Ray—it*

seems the questions are being aimed mainly at the orthopedist and neurosurgeon. I think that is probably because they may be more vulnerable. Dr. Ray, what are your criteria for performing myelography?

DR. RAY: As I said earlier, I don't ordinarily use myelography except under special circumstances, the most important of which would be to differentiate a neoplasm. There are times when a neoplasm may simulate ruptured disc in symptomatology and physical findings so closely that it is virtually impossible to tell the difference unless one, somehow or other, gets a suspicion or some notion that all is not quite as it should be for a typical ruptured disc syndrome. In those patients I would certainly use myelography.

From the point of view of the patient's satisfaction and the satisfaction of his well wishers (perhaps his physician or his family), it may be desirable on rare occasions to demonstrate the presence of a disc by myelography before proceeding with an operation. Or it may be advantageous to demonstrate that he does not have one, at least one big enough to show on a myelogram.

MODERATOR CLEVELAND: *Here is a question that is simple, so your Moderator feels himself almost qualified to answer it: What is the best method of protecting the skin before applying adhesive strapping?*

I take it they mean the lower back, when the skin is sensitive to the adhesive tape. Simply paint the skin with tincture of benzoin and it usually protects it very well. Let the benzoin dry thoroughly before applying the adhesive tape.

I would like to ask Dr. Thomas if he will briefly outline, if it is possible to be brief under these circumstances, the plan for treatment of psychogenic low back pain.

DR. THOMAS: The plan begins by fixing in mind as clearly as one can the probable scope of the structural pathology. I think after that it is best to leave the local complaints system aside and work with the personality in terms of its other problems and broader emotional factors. That is accomplished by taking the psychiatric history and doing the psychiatric examination in the regular medical school sense mentioned by Dr. Bosworth.

I like to think of this study of the patient as taking place in two stages: first, a who's who. This is the part of the history where one finds out what manner of person this is, where he has been, what he has done,

what his home life is, the way he has met the external facts of life. That should be in the history. Then we turn on another radio system inside of us and listen to the implications, and that part can be compared to a kind of blind man's buff or those children's games where they say "warm, warm, warm" when you are getting near the hidden object, or "cold, cold" when you are getting further away. You get the feeling of getting warm, or the patient gets the feeling he is getting warm, and then you swoop out more into that part of the history. After allowing the person to pour forth in this manner for a considerable period of time, a figurative pressure is often taken off that root, just as Dr. Bosworth and Dr. Ray are taking the physical pressure off that nerve root.

MODERATOR CLEVELAND: *I have two questions for Dr. Bosworth. What about fibrositis of the lumbar area as a cause of low back pain? Is there such a condition as a tear of the lumbar fascia due to trauma as a cause of pain?*

DR. BOSWORTH: Certainly a tear of the lumbar fascia can cause pain. We know the patient has pain after we have incised the lumbar fascia during a spine fusion. Such conditions heal and recover with the speed and in the sequence in which the incision or laceration trauma recovers in the body and the fibrous tissue eventually disappears. I believe true fibrositis in the lumbar area is really another myth, although I can conceive of its occurring. I would think, rather than fibrositis of the lumbar region, one might have a mild fasciitis, an irritation of the musculature from reflex stimulation, and prolonged contracture for protection of other pathology such as a disc or underlying disease.

MODERATOR CLEVELAND: *We are about to close this panel discussion with one more question for each of the panelists.*

Dr. Bosworth, if there is purely mechanical or structural cause for low backache, what percentage of completely satisfactory results is achieved by surgical intervention?

DR. BOSWORTH: Where we have had purely mechanical conditions, as disc lacerations and herniation, we have excellent and satisfactory results in 88.6 per cent of cases where a solid fusion was obtained, that is, the patients were free of pain and had normally stable backs with no weakness.

MODERATOR CLEVELAND: *Dr. Ray, would you care to speak further on the results which you showed us on the screen?*

DR. RAY: I have little to add. I certainly meant to imply that the

patients were carefully selected for operation. I am careful not to choose for operation a patient who I think has some complicated back trouble and especially so if I think he may require a spine fusion. I have performed fusion in conjunction with removal of the nucleus pulposus in a series of patients and I still occasionally do a spine fusion if I find it is necessary at the time of operation. But if I can anticipate it in my evaluation of the patient, I send that patient to Dr. Bosworth or to someone who will do what is necessary. It takes time to operate on a back, to deal with the abnormal disc and then do an adequate fusion. The results that I have reported do not imply that everyone is free of all backaches and pains after having his nucleus pulposus removed, but the figures do imply that in the type of patient whose symptoms I have described to you, the results are as good as one could reasonably hope to attain.

Dr. Thomas has made very pertinent remarks about back pains and how they may fall into the field of psychological disorders. I am often inclined to compare the patients complaining of backache that goes on and on, or keeps recurring in spite of anything we can do, with those who complain of a chronic headache after they have had a head injury. This common complaint falls into the much overworked category of post-traumatic syndrome. Many people, physicians included, look surprised when it is pointed out to them that it is impossible to hurt a head in such a way that there will be a permanent or recurring headache over a period of years. It is understandable that a headache may persist for a few weeks or months as the result of a bump, hemorrhage, or cut, or whatever, but there is no traumatic alteration that can produce a permanent headache. My guess is that if we were not so aware of the many possibilities as causes of backache, we would recognize the fact that there are many people who, once having hurt their backs, expect to have backaches forever and ever. The mechanism in many is probably related to muscle tension. To say then that a patient had a poor result following removal of a herniated nucleus pulposus because he still has backaches is not quite fair, no more fair than it is to say that a patient has had a poor result who complains of recurring headaches for the rest of his life after he has had an extradural hematoma evacuated or depressed skull fracture repaired. Perhaps the comparison isn't entirely appropriate in every respect but it is one that often comes to mind.

MODERATOR CLEVELAND: I think you have stated that very well

indeed, Dr. Ray.

Now I should like to ask Dr. Aldridge this question: Given patients with low backache, which in your opinion may be due to uterine prolapse, retroversion of the uterus, ovarian or uterine tumors, which may be classified as mechanical causes, approximately what percentage may be relieved by surgical procedure?

DR. ALDRIDGE: Earlier in this discussion attention was called to certain reliable clinical studies which have shown that four out of five women with low back pain due to retroversion can be cured by operations to correct their uterine displacements.

Women who have uterine prolapse complain frequently of low back pain and a dragging sensation in the pelvis. It is known that their symptoms are due to relaxation of structures in the so-called upper pelvic floor, by which the uterus is supported at the normal level in the pelvis. Clinical studies have shown that low back pain due to uterine prolapse can be relieved by vaginal plastic surgery in 80 to 85 per cent of patients who have such conditions.

It seems obvious that benign uterine tumors and ovarian tumors or cysts should be removed if they are large enough to cause low back pain by mechanical pressure. I doubt that there are any statistics to show the percentage of patients who can be relieved of low back pain by operations for such conditions. It seems reasonable to assume, however, that close to 100 per cent of these patients should be cured as soon as the causes for their symptoms have been removed.

MODERATOR CLEVELAND: *I shall address the final question to Dr. Thomas: In cases of psychogenic low back pain, what percentage of cures may the psychiatrist expect?*

DR. THOMAS: I am unable to answer the question. The patients whom we have followed through in this condition, often with happy results, have been extremely carefully screened. Our colleagues have provided us with such well chosen referrals, such well planned consultations, that any estimate made of the number that we have been able to help would be very misleading.

MODERATOR CLEVELAND: I want to thank all of the members of the panel for taking part in this very excellent discussion of low back pain.

NEW YORK PATHOLOGICAL SOCIETY

Presented at the Meeting on May 22, 1958 at The New York Academy of Medicine

THE BASIS OF CONVULSIVE ATTACKS IN CHILDREN—AN EXPERIMENTAL STUDY*

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A clinico-anatomic study of 21 children, all under five years and most under one year of age, who succumbed to severe and persistent convulsions, disclosed one or more of the following important associated clinical findings: 1) fever; 2) respiratory difficulty; 3) severe malnutrition; 4) hypoglycemia. Evidence of widespread injury to the cortical ganglion cells was found at necropsy in each instance, with special predilection for Sommer's band of the Ammon's horn formation (Figure 1), the occipital and sometimes the parietal cortex (Figure 2), and the Purkinje and granular cells of the cerebellar folia (Figure 3).

In ten additional cases of birth injury, in which asphyxia but not convulsions was a prominent feature, similar anatomic findings were observed in the nervous systems. These findings, usually designated as necrobiotic, have long been recognized as resulting from cerebral anoxia or hypoxia. The suggestion, therefore, that anoxia was the factor responsible for the cerebral injury acquired during the convulsive attack seemed amenable to experimental proof.

Experimental Metrazol Convulsions. Some years ago Dr. Lincoln Opper and I undertook a study of the effects of repeated convulsions in cats on the cytology of the cerebral cortex. We succeeded in demonstrating that oft repeated and prolonged convulsions injured cortical neurones (the Purkinje cells were especially vulnerable) and that these changes were more readily produced in young kittens than in older cats (Figure 4). To demonstrate these changes with the usual staining methods, it was essential that the animals survive the convulsive attack

* Manuscript received May 1959.

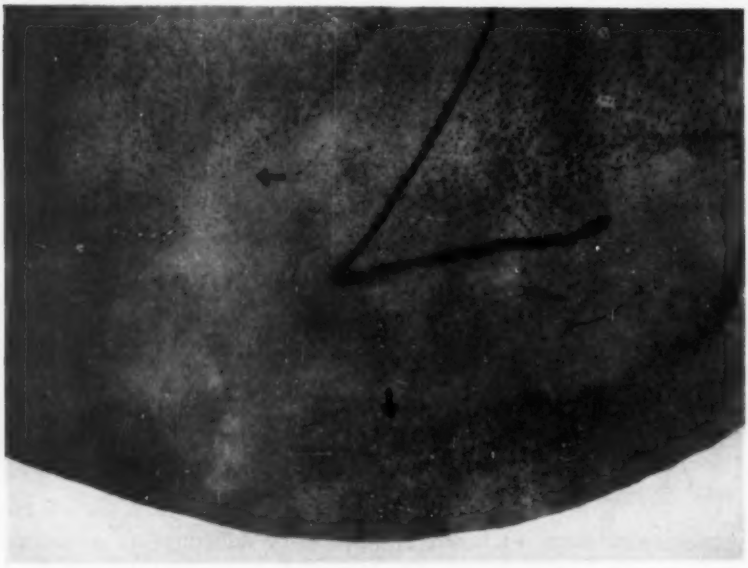

Figure 1—Loss of cells in Sommer's sector (between arrows) of cornu Ammonis formation. Nissl stain; X16.

by at least 10 and preferably 24 hours. Repeated convulsions produced a summation effect on the extent of the cortical injury. Both camphor and thujone (oil of wormwood) were found just as effective as metrazol in producing the convulsions as well as the cortical neuronal injury.

For many years, these and other convulsive drugs have been employed to study the experimental counterpart of the spontaneous epileptic attack in man[1]. Just as in the human attack, there is a momentary aura of apprehension when the animal remains rigid, ceases to struggle, and has striking blanching of the mucous membranes. Then there is a cry, which is followed almost immediately by the onset of generalized severe tonic-clonic motor activity. Tongue-biting, if precautions have not been taken to prevent it, can be severe. The duration of the convulsive attack is dependent on the amount of convulsant administered, but there is a considerable individual susceptibility or resistance. The muscular contractions may last 30 seconds or as long as two minutes, then there is a pause which is followed again by tonic-clonic contractions. With a large dose of convulsant, these attacks may recur for 10 minutes or longer and have the appearance of status

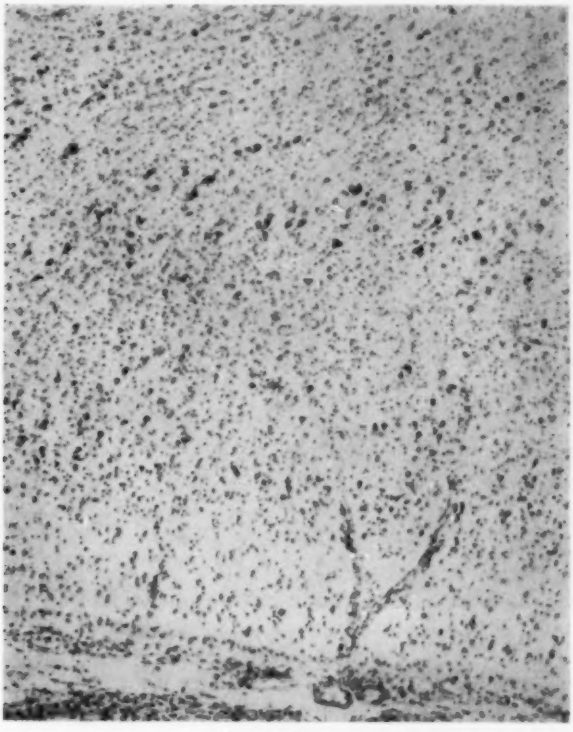

Figure 2—Widespread necrosis of ganglion cells in parietal lobe cortex. Nissl stain; X65.

epilepticus. Each series of spastic contractions is more feeble than the preceding, until these cease altogether.

The mucous membranes now have taken on an intense cyanotic hue and it is noticed that apnea is striking, respirations being only five or six per minute. During the height of the attack there is much breath-holding for as much as a minute at a time, during which cyanosis deepens, then breathing starts again, quite deeply and slowly. At some time during the attack the animal lost control of both bladder and bowel sphincters. The pulse is thready and rapid. With the cessation of the motor phase of the convulsion the animal appears to be in a deep sleep from which it can be aroused only with painful stimuli. Gradually all the reflexes, including the corneal, which were abolished, return and the animal begins to rouse. After a particularly severe attack the animal may

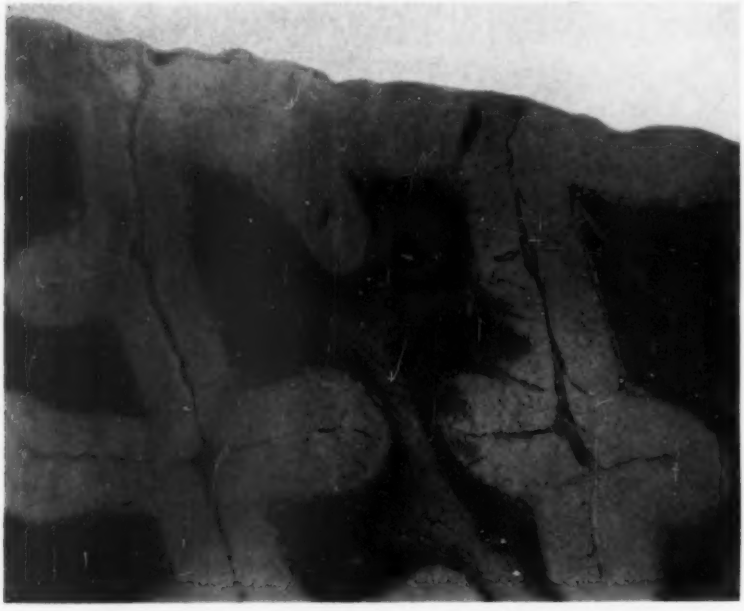

Figure 3—Loss of Purkinje cells and hemorrhages in molecular layer of cerebellar cortex. Nissl stain; X24.

appear dazed for a period up to six hours.

Increased Thoracic Pressure as a Factor in Cerebral Anoxia. The previous experiments had shown that the breath-holding and apnea were associated with measurable increases in both the intrathoracic pressure and the cerebrospinal fluid pressure. It seemed a logical step, therefore, to determine whether comparable increases in these pressures, without the intercedence of convulsant drugs or convulsions, could produce the same kind of cerebral anoxic changes. Accordingly, Dr. Starrey Branning and I devised an experiment with cats in which simultaneous readings were obtained of the intrathoracic and spinal fluid pressures as well as of the respiratory rate (Figure 5).

Under light sodium pentobarbital anesthesia the respiratory excursion is from minus 5 to 0 cm. of water pressure, the spinal fluid pressure is 20 mm. of water and the respiratory rate 20 per minute. As air is injected into the pleural cavity through a needle in the intercostal space, the respiratory rate gradually rises; so does also the spinal fluid

Figure 4—Photomicrograph of cortex of cat's brain following repeated metrazol convulsions. There is relative sparing only of layers 5 and 6. Nissl stain; X60.

pressure, but at a much more rapid rate. The respiratory excursion diminishes from minus 1 or 2 to plus 1 or 2 cm. As about 160 ml. of air are injected, the shallow respirations, which had risen to 50 per minute, drop to five per minute, or cease altogether; the intrathoracic pressure rises at the same time to plus 2 or 3 cm. and the respiratory excursion, if at all measurable, is about 1 cm.; the spinal fluid pressure is 110 mm. This precarious balance can be maintained for 10 minutes or more by alternately aspirating and injecting air into the pleural cavity.

By this means alone, without the intercession of convulsive attacks, it was possible to reproduce the necrobiotic cortical lesions seen both in infants and experimental animals with convulsions (Figure 6).

Experimental Febrile Convulsions. Hyperpyrexia seemed to play an important part in initiating convulsive seizures in a number of the

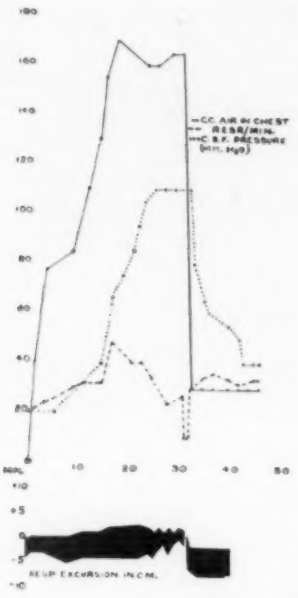

Figure 5—Graph of respiratory excursion and spinal fluid pressure in cat under light Nembutal anesthesia with increasing amounts of air injected intrapleurally and consequent rises in intrathoracic pressure.

infants who had a fatal outcome and in whom widespread neuronal destruction was found in the cerebral and cerebellar cortices. This experience was paralleled in an experimental study with kittens undertaken by Dr. Margaret Lennox, Dr. William Sibley and me several years ago[2]. The animals were subjected to elevations of temperature (42.9°C.-43.0°C.) by external heat in a radiant-heating chamber. Convulsions occurred almost exclusively in kittens between 5 and 8 weeks of age and were determined primarily by the height and the rapidity of rise of the fever. Not all kittens convulsed. Mortality was highest when convulsions did occur, when fever was prolonged, and in kittens of four weeks of age or younger. Neuronal changes consisted of hyperchromasia, shrinkage and, ultimately, liquefaction. They occurred in the cerebellum most conspicuously and consistently, then in the occipital lobes. The frontal and parietal lobes were less often involved, and the basal ganglions, pons and brain stem were spared. Only those kittens which survived the seizures by 12 hours or longer

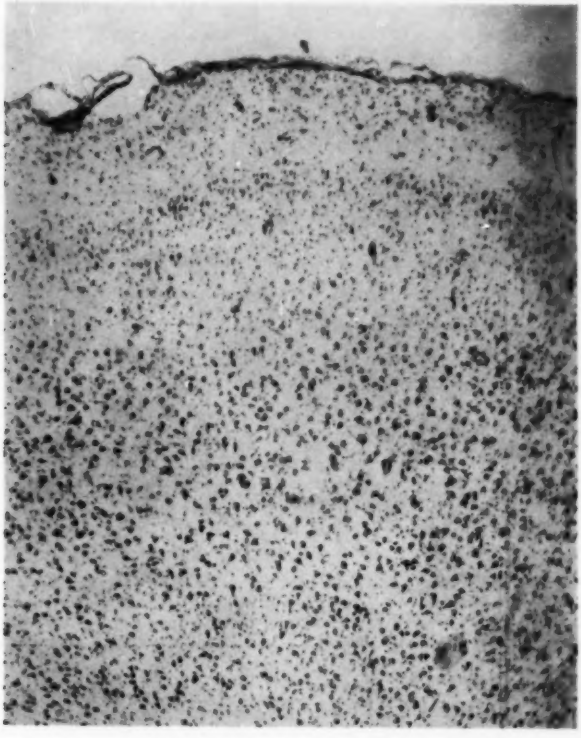

Figure 6—Loss of neurones in laminae 2 and 3 with injury to those in deeper layers of cortex following repeated respiratory arrests in cat subjected to rises in intrathoracic pressure. Nissl stain; X60.

showed these changes in their nervous systems. It must be added that these cellular changes were indistinguishable from those observed in the fatal cases of hyperpyrexia with convulsions in infancy.

Experimental Hypoglycemia. Three of the young children with convulsive attacks suffered from extreme malnutrition and had lost an appreciable proportion of their body weight prior to the onset of the fatal seizures. Three additional infants who were admitted to the hospital in convulsions were found to have strikingly reduced blood sugar levels. Unfortunately, this observation came to light immediately before death, when intravenous glucose was of no avail, or shortly after death. It is worth noting here that young infants on a milk diet will have a galactosemia which can mask the low blood glucose levels[3].

Figure 7—Photomicrograph of normal (control) cat's brain above that of experimental animal which survived severe hypoglycemic convulsions. Note extensive loss of neurones (lighter staining) in cortex and basal ganglions in experimental as compared to control animal. Nissi stain; X ca. 5.

To test the effect of hypoglycemia on the production of convulsive attacks in animals and possible cerebral injury, Dr. Herman Yannet and I undertook the following study[4]. Cats were injected with 15 to 20 units of insulin per kilogram of body weight and blood was withdrawn at intervals for glucose determinations. It was found that in somewhat more than half of these animals a drop in blood sugar to much below 50 mg. per cent was followed by severe tonic-clonic seizures. These could be interrupted promptly by the administration of intravenous glucose, or more slowly by injecting glucose via a stomach tube. The convulsive attacks, if allowed to run their course without treatment, amounted to status epilepticus and in every important detail resembled the seizures produced with metrazol. The resulting cerebral lesions were quite similar to those produced with the convulsant drugs and with hyperpyrexia, but they were always more severe and widespread. Several of the animals which survived severe convulsions and a prolonged state of hypoglycemia had lost most of the neurones in the cortex

of both cerebrum and cerebellum (Figure 7).

But not all the animals convulsed. Some, indeed, lapsed into a deep coma from the start, and this alone was indicative of cellular damage. With or without convulsions, the strikingly reduced blood sugar levels resulted in neuronal destruction. Before this fact became clear, when it was thought that the seizure was the most important element in cerebral injury, sodium pentobarbital or intravenous sodium amobarbital was employed in some animals to control the attacks. It was soon discovered, however, that anesthesia enhanced the injury rather than prevented it. Presumably this was due to a further depression of the metabolism of the ganglion cells of the brain, which was already depressed by the low glucose level. It is, of course, well known that the only important source of energy of cerebral ganglion cells is glucose.

Summary. Three facts have been established by these experiments. One is that convulsions, regardless of how they are initiated, produce cerebral anoxic changes which can destroy cortical ganglion cells in the cerebrum and cerebellum. A second is that hypoglycemia, even without producing convulsions, can destroy neurones by lowering glucose levels below critical points. The third fact is that the cerebral lesions described in both infants and experimental animals result from the convulsive seizures and do not cause these seizures.

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DISCUSSION

LOUIS ODESSKY: I should like to ask Dr. Zimmerman two questions: Does the damage to the cells remain permanent, or is it at a level at which it may be reversible and the cells regenerate? Do you get the same type of picture in electroshock therapy?

H. M. ZIMMERMAN: Dr. Odessky asks if the damage to the ganglion cells is permanent, or if they reconstitute themselves, and the answer is that they do not.

As you saw in the child who survived six months, the ganglion cells have permanently disappeared and scar tissue has replaced them in the form of gliosis. We are born, I suppose, with all the ganglion cells we shall ever have, and they get larger as we grow, but if they are damaged by anoxia, I think they are damaged irreparably and disappear.

In electroshock the amount of interference with cerebral metabolism, with ganglion cell metabolism, and the amount of respiratory distress are evidently considerably less than are produced by very severe insulin convulsions. The several cases of electroshock therapy which I was privileged to see had nothing like this damage. I ought to mention now that I do not believe that the usual insulin shock therapy cases have anything like this. You noticed that we have to have certain rather drastic conditions: the blood sugar levels have to be way down; the convulsions have to be very severe and have to last a relatively long time. I do not believe in most instances such conditions are achieved under therapy. I will say, however, that I have seen spontaneous damage to the cerebral cortex in hypoglycemia with islet cell adenomas of the pancreas, and I have seen similar changes in two patients in whom very severe insulin convulsions were induced.

LOUIS ODESSKY: What happens to the cortex in cardiac arrest, where the patient has been anoxic for quite a few minutes up to a few hours?

H. M. ZIMMERMAN: I tried to emphasize that the patient must survive for a minimum of 10 to 12 hours before any of the changes are demonstrable morphologically, because the cells may be damaged and may not show it. If the cardiac arrest lasts for two to four minutes with survival, and then eventually a postmortem is done, changes of the kind I have described with convulsions are seen. A better example than cardiac arrest is the respiratory arrest during nitrous oxide anesthesia, in which we see all the changes I have shown with convulsions.

ABNER WOLF: Dr. Zimmerman's beautiful demonstration of the effect of convulsions on the brain of both animals and man is similar to what Dr. Cowen and I observed in a study of a large group of children who had suffered brain damage, and in whom convulsions obviously seemed to be the cause of the damage. In this regard I would like to point out that neurologists often have taken a skeptical attitude toward the effect of convulsions on the brain, because they see adult patients who have convulsed over a long period of years and who have shown no deterioration. As Dr. Zimmerman has pointed out, repeated, severe convulsions occurring in rapid sequence, are needed to produce these changes in the child's brain. The fact that they do not occur in the adult does not affect the validity of the present findings.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on May 22, 1958, at The New York Academy of Medicine

Biological Effects of 6-Aminonicotinamide

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Before discussing 6-aminonicotinamide (6-AN), we would like to summarize some of the information we have about the metabolism of nicotinamide and nicotinic acid, with particular reference to malfunction of the central nervous system. Nicotinic acid is necessary for cellular life and is required by all living cells. In animal tissues almost all of the nicotinic acid is found in the nicotinamide moiety of the two coenzymes, di- and triphosphopyridine nucleotide (DPN and TPN). The pyridine nucleotides are presumably universal constituents of animal tissues. DPN and TPN are known to be involved in at least 35 different enzymatic reactions, including the anaerobic breakdown of carbohydrates, the citric acid cycle, the deamination of glutamic acid, and photosynthesis.

Neurologic disturbances have been noted in human beings with nicotinic acid deficiency. Since the nucleotides are required for reactions by which the brain secures energy from such fuels as fructose, the alteration of such reactions may be involved in the clinical abnormalities. This hypothesis, however, has not been proven. Other serious metabolic disturbances occur in nicotinic acid deficiency, but in no instance has it been possible to relate any specific biochemical disturbance involving nicotinic acid coenzymes. Indeed, since pellagra is usually a mixed deficiency, it is not surprising that there is good evidence that the neurologic changes in pellagra are related to a concomitant thiamine deficiency.

The determination of the essential role of nicotinic acid in the nutrition of mammals is complicated by many factors. A few examples are worth noting. Tryptophan is a precursor of nicotinic acid not only in the rat but in man and other mammals. The formation of nicotinic acid from tryptophan occurs so readily in the rat that a nicotinic acid deficiency has not been demonstrated. In fact, rats accumulate in their tissues more nicotinic acid than they ingest. Given an adequate amount of tryptophan, rats will thrive on a pellagra-producing or nicotinic acid-deficient diet.

The conversion of tryptophan into nicotinic acid *in vivo* introduces a second complication, since it requires the mediation of a pyridoxine-dependent enzyme system. Thus, in pyridoxine deficiency there is an interference with the formation of nicotinic acid from the amino acid precursor.

Nicotinic acid is also related to vitamin A activity. In the retina, which, incidentally, contains one of the highest concentrations of DPN, the coenzyme is necessary for the conversion of vitamin A to the visual pigment, rhodopsin. Yet there is no indication that patients with pellagra, or that nicotinic acid-deficient animals have visual defects. Hundley[1] has pointed out that this is one of those anomalous situations wherein a seemingly clear-cut biochemical ex-

planation exists for a defect that is not known to occur. This is akin to the "orphan" viruses for which there is no known disease.

There is little or no relationship between the severity of nicotinic acid deficiency and the blood level of nicotinic acid or of DPN. The content of the vitamin or coenzyme in liver or muscle generally shows a better correlation with the clinical state than do blood levels. Indeed, nicotinic acid levels in the blood may be depressed in pathologic states other than nicotinic acid deficiency.

The precise determination of the sequence of events involved in the pathologic changes occurring in nicotinic acid deficiency is obviously complex. Inhibitory metabolite analogues are providing new tools for this analysis. In 1938 Woolley[2] demonstrated that 3-acetylpyridine (3-AP) was toxic in nicotinic acid-deficient dogs, while in equivalent doses it was without effect in normal dogs. In later experiments[3] with mice he produced a pellagra-like deficiency with the compound which could be prevented by nicotinamide. The changes which occurred in mice included reddening of the skin and tongue, loss of control of hind legs, and eventual paralysis. In later work with dogs McDaniel, Hundley, and Sebrell[4] showed that the effects of 3-AP were almost paradoxically complex. Depending on the dose and the time of administration, 3-AP could protect against the development of black tongue or even cure the disease. Under other circumstances the agent produced a toxic syndrome in nicotinic acid-deficient dogs which caused paralysis and death. The toxic syndrome was irreversible, even though the agent was discontinued and large doses of nicotinic acid were administered. The toxic syndrome was quite different from the disturbances seen in dogs in which nicotinic acid deficiency was produced solely by dietary deprivation.

A possible explanation for these apparently anomalous findings comes from the work of Kaplan and associates[5]. On the one hand they showed that, in the liver of mice, 3-AP is detoxified to nicotinamide and this in turn is utilized for the formation of hepatic DPN. This could explain the preventive and curative effectiveness of 3-AP in nicotinic acid deficiency. On the other hand they showed that animal tissue DNPases catalyze exchange reactions between the nicotinic acid moiety of DPN and compounds related to nicotinamide. Thus, in the spleen and brain of mice given the agent, the 3-AP analogue of DPN was formed. In the liver of mice, the detoxification of 3-AP occurs so rapidly that such exchange reactions could not be detected.

Kaplan's explanation of the toxicity of 3-AP is as follows: The liver can convert 3-AP to nicotinic acid or nicotinamide at an appreciable but limited rate. When the rate of hepatic conversion is exceeded, other tissues, especially the brain, incorporate the analogue by way of the DPNase system. Since the exchange reaction has been demonstrated *in vivo* in the brain of the mouse, it is reasonable to suggest that production of the false DPN is responsible for the neurotoxicity of 3-AP. Incidentally, this mechanism of intoxication is an example of pharmacodynamic actions which R. A. Peters[6] has classified as "lethal syntheses". In effect, metabolite analogues, not in themselves toxic, can enter into anabolic pathways identical with those followed by the respective metabolites. The analogues are then biosynthetically converted into more complex substances with capacity to interfere with specific enzymatic reactions.

Johnson and McColl in 1955[7, 8] first described the toxicity of 6-AN in a number of animals in which the agent proved to be more potent than 3-AP. In rats, effects were produced which they considered to be like those seen in niacin deficiency. Among these was paralysis of the extremities. They also showed that the simultaneous administration of nicotinamide or nicotinic acid could prevent intoxication. In 1956 Johnson[9] demonstrated that the 6-AN analogue of DPN could be isolated from an incubated mixture of pig brain DPNase, DPN, and 6-AN. The analogue was also found in the liver and kidney of mice and in the Walker 256 tumor in rats given 6-AN.

A series of experiments was performed in our laboratory with rats and mice to obtain data concerning the range of effectiveness of nicotinamide in preventing deaths from 6-AN toxicity. In CFN male rats, the

LD_{50} of 6-AN was found to be 9 mg./kg. when given intraperitoneally. At a dose of 20 mg./kg. (2.2 x LD_{50}), 50 per cent of the animals were fully protected by giving 3.3 mg./kg. of nicotinamide intraperitoneally immediately before the dose of the antimetabolite. Larger amounts of the vitamin protected all animals. In similar experiments with ICR male mice, the LD_{50} was 50 mg./kg. The dose of nicotinamide with which 50 per cent of the animals could be protected against 100 mg./kg. (2 x LD_{50}) of 6-AN was 6 mg./kg. It can be seen that relatively small amounts of the vitamin are needed to prevent the antimetabolite's toxic effects.

In 1957 two groups of workers[10, 11] showed that 6-AN had inhibitory activity against several experimental tumors. We instituted a toxicologic study in order to obtain information essential to its clinical trial. The course of intoxication and the pathologic changes, which were related primarily to the central nervous system in rats, cats, and dogs, have been briefly described in a preliminary report[12]. The details of the neuropathologic effects will be described by the next speaker. We would like to make brief mention of the changes outside the central nervous system. In rats, abnormal germinal epithelial cells were observed in the testes, and with this, diminished spermatogenesis. A moderate degree of bone marrow depression was seen after ten days. In dogs, a similar type of testicular damage was present, but no bone marrow damage. In the buccal cavity of the latter, inflammatory reactions were seen with superficial ulcerations. The tongue contained telangiectatic submucosal capillaries.

It is interesting to note that a varied pattern of response occurred in animals given the same dose. In a group of dogs receiving daily injections of 4 mg./kg. intravenously, one animal obtained ten doses without apparent effect; others receiving the same number or even fewer became paralyzed. A possible explanation for such differences in response may be variations in the level of nicotinamide present in the animals at the time of the experiment.

Preliminary clinical trials at two institutions have resulted in a variety of toxic effects, including neurologic disorders. It appears unlikely that 6-AN will have any clinical value.

In the present state of our knowledge, it is reasonable to attribute the neurologic damage caused by 6-AN to the formation of a poisonous, DPN-like moiety in selected cells of the central nervous system. Such a mechanism, however, does not explain why these particular cells are the susceptible ones. After all, DPN and TPN are essential for the metabolism of all tissues or cells, and the coenzyme-synthesizing enzymes are undoubtedly distributed widely. Quite obviously the full explanation of the specificity of action of 6-AN still remains to be determined. Moreover, we believe that at present we are accumulating information that is pertinent only to explanations of antimetabolite effect; it remains to be proved whether such data explain effects seen in naturally occurring or experimentally induced nicotinic acid deficiency.

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Pathological Changes in the Central Nervous System Produced by 6-Aminonicotinamide

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Johnson and McColl[1] found that 6-aminonicotinamide (6-AN) was extremely toxic to rabbits and rats, causing paralysis of the extremities and blindness. Morsiani and his co-workers[2, 3] later noted a paraplegia or a tetraparesis in mice, and Halliday, Sloboda, Will and Oleson[4] recorded paralysis in rats following the administration of this substance. Rats, cats and dogs inoculated with 6-AN by sternberg and Philips[5] showed a variety of neurologic abnormalities, chief among which were motor disabilities. They demonstrated striking degenerative changes in the gray matter of the anterior horns of the spinal cord and of the nuclei of the brain stem. We have had the privilege of further studying tissues from these animals and have added a series of rats and cats of our own.

The combined data in 16 rats indicated that, when they were inoculated intraperitoneally with 8 mg. of 6-AN per kilogram of body weight, they showed neurologic manifestations within 24 hours. A few showed impairment of placement reactions in the hind limbs with extension and stiffness in these extremities as early as six to eight hours. A small group of rats which received higher doses, ranging from 16 to 64 mg. per kg., administered intraperitoneally, became sluggish three hours following the inoculation and developed weakness in the hind limbs in from three to five hours. The treated animals became increasingly lethargic and hypoactive, gradually lost their placement reactions in the hind limbs and showed poor righting and labyrinthine responses. They became increasingly unsteady, evidenced weakness in all limbs, the hind limbs always seeming more affected, were reluctant to move and came to lie on their sides with hind limbs extended. Some exhibited intermittent rapid rhythmic movements of the limbs and head. There seemed to be no impairment of vision or audition. Movements of the head were best preserved. Toward the end, swallowing and respiratory difficulties of minor degree were noted. Response to pinching and pin-prick of the skin and tail gradually decreased. Convulsive seizures were not observed. All the animals in this group were sacrificed in from one hour to ten days.

Four cats were studied. One of these was inoculated intravenously with 30 mg. of 6-AN per kilo and was observed to retch and cough at three hours. This animal developed difficulty in movements of the hind legs at four and a half hours and was unable to stand at two days. Three cats which received 30 mg. of 6-AN per kilo intraperitoneally developed signs within nine hours. These included retching and vomiting, weakness of the hind limbs, tremors, unsteadiness, loss of response to pinching and pin-prick, apparent loss of hearing in one case and variable generalized weakness. Two cats were sacrificed at five days, one at nine days, and one at 20 days.

Two dogs repeatedly inoculated intravenously with 4 mg. of 6-AN per kilo showed no abnormal signs for several days, then developed a paralysis of the limbs, more marked in the hind legs, while the reflexes remained active. One, receiving six daily injections, was sacrificed at eight days and the other, that received seven injections, was sacrificed at ten days.

Rats sacrificed at one hour, three hours, six hours, nine hours, 24 hours, two days, three days, four days, eight and ten days following the administration of 6-AN showed the following changes in the nervous system. The spinal cord was consis-

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tently affected, the anterior horns being predominantly involved. Nearly all levels examined showed lesions in the gray matter, with some intensification of the changes in the lumbar region. The white matter of the spinal cord, the spinal roots and ganglia and the peripheral nerves were unaffected. Many of the nuclei of the medulla, pons and midbrain and the roof nuclei of the cerebellum were affected as severely as were the anterior horns of the spinal cord, although there was some variability in this involvement, as there was in that of various spinal cord levels. Here again the white matter was spared. Focal lesions were encountered in the geniculate bodies, thalamus and corpus striatum. In general the lesions were marked by their sharp localization and distinct outlines, often corresponding to a single nuclear mass or to a fraction of it. The central portions of the anterior horns were most regularly involved. Often, however, the process affected all of an anterior horn and overflowed into the posterior horn.

The earliest reliable histologic changes were observed at two days following inoculation. It must be noted that neurologic abnormalities appeared as early as three to six hours and it is clear that functional derangement antedated the pathologic changes. In the one day post-inoculation rats, only fresh petechiae in the susceptible areas of the gray matter were encountered and these were not constant. On the second day, occasional changes in the walls of small vessels, chiefly arterioles, accompanied the hemorrhages. These consisted of swelling of mural cells, impregnation of the wall with fibrin and perivascular fibrin. Pallor of nerve cells in these regions was an equivocal finding and one which needs further documentation. On the third day, the affected gray matter showed chromatolysis or necrosis of nerve cells, mild polymorphonuclear infiltration of the walls and perivascular spaces of small vessels in the affected gray matter, with mild diffuse neutrophile infiltration of these areas. On the fourth day, pallor, chromatolysis, swelling and, less often, necrosis and disappearance of nerve cells were well advanced, and microglial and vascular reactions were increasingly prominent. The tissue began to be loose-meshed, loculated and with fresh petechial hemorrhages still occurring in it. One very striking feature was the frequent preservation of nerve cells at the margins of severe lesions or, less often, in their depths. The vascular reaction was chiefly an endothelial hyperplasia, with little increase in connective tissue fibers in the small vessels. The microglia passed through the usual reactive phases in advancing toward macrophages in response to the nerve cell destruction. Axones and myelin sheaths underwent degeneration within nuclear masses. The astrocytes appeared to suffer injury, as did the nerve cells, but to a lesser degree. They failed to react properly and showed evidence of disintegration.

The lesions in the cats and dogs were generally of the same type and distribution, with variations which seemed to be dependent in part on the dosage. In the cats, occasional changes in the cerebral cortex, mild in degree, were found, principally in the ventral portions of the cerebrum. There was secondary degeneration of axones and myelin sheaths in anterior roots and in part of a sciatic nerve in the longest-lived cat.

The lesions produced by the administration of 6-AN to rats, cats and dogs appear to be confined to the gray matter of the central nervous system, sparing its white matter and that of the peripheral nerves (except for secondary degeneration). This is in contrast to the changes which have been described by Hicks[6] in the nerve cells of the spinal and sympathetic ganglia with another nicotinamide antagonist, 3-acetyl pyridine. No lesions were described by Hicks[6] in the spinal cord, whereas this was a prominent site of destruction of nerve cells following the administration of 6-AN to rats.

Hicks[6] observed necrosis of the adrenal medulla and striated muscle with 3-acetyl pyridine, and changes in other organs have been reported following the administration of 6-AN. These have included atrophy of the lymph follicles in the spleen, with a marked reduction in its size, adrenal and hepatic degenerative focal lesions, atrophic lesions of the mucosa of the tongue, changes in the intestinal mucosa, testicular involvement and other changes[8]. In our animals,

the only consistent findings established thus far were in the testes and spleen.

Johnson and McColl[1] found that the simultaneous administration of nicotinamide in mice markedly increased the minimal lethal dose of 6-AN. Halliday, Sloboda, Will and Oleson[4] reported the prevention of symptoms due to the administration of 6-AN by the addition of niacinamide to the diet. They referred to the loss of motor control, paralysis, kyphosis, anorexia, diarrhea and bloody urine in their rats as niacin deficiency symptoms. The lesions produced in the nervous systems in our rats, cats and dogs do not resemble those that have been reported with nicotinic acid-deficient diets. The posterior column and pyramidal tract degeneration of axonal chromatolysis in the Betz cells, anterior horn cells and cells of the columns of Clarke and of degeneration of the peripheral nerves, as described in human pellagra by Zimmerman, Cohen and Gildea[7], were absent in our animals, and it is difficult to make any adequate comparisons with those in canine black tongue because of the confusing variety of changes in the nervous system that have been reported in it.

In considering the mechanism by which the nervous system was damaged by the administration of an earlier nicotinamide antagonist, 3-acetyl pyridine, Hicks[6] concluded that the lesions represented an accelerated picture of nicotinamide deficiency, and that the cells involved are specifically more dependent on pyridine nucleotide enzymes, of which nicotinamide is a prosthetic group, than other cells.

In the case of 6-AN it has been suggested[1] that its delayed action when inoculated into animals, as well as its lack of activity when added to tissues *in vitro*, implies that its action is dependent upon prior metabolic transformation *in vivo*, possibly its incorporation into pyridine nucleotides (diphosphopyridine nucleotide-cozymase) in place of nicotinamide, yielding the corresponding 6-aminonicotinamide analogue. This could exert a toxic effect by depleting the tissues of pyridine nucleotides. It might also inhibit the numerous enzyme reactions, in which the pyridine nucleotides function as coenzymes, by competing with the latter for active sites on the enzyme. This might produce profound effects on cell metabolism in areas especially sensitive to such enzymatic dysfunction and might lead to destruction of gray matter to the degree and in the pattern seen here.

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DISCUSSION

H. M. ZIMMERMAN: Since Dr. Wolf mentioned some of the work on deficiency diseases which I did some years ago, I may state that the lesions produced with nicotinic acid deficiency were complicated, as suggested by Dr. Sternberg, by thiamine, pyridoxine and other vitamin deficiencies, and our animals did not survive long enough, as a consequence, to produce the massively destructive lesions Dr. Wolf has just shown you. In none of the animals with diarrhea, dermatitis, and finally with peripheral neuropathy, did we find lesions so widespread as to involve the anterior horns of the spinal cord and the various cranial nuclei. It is true that, at least in the midbrain, the lesions described by Dr. Wolf are strikingly similar to those we originally produced. Perhaps his type of experiment is ideal in that we can study the effect of nicotinic acid deficiency alone, without the complications of other deficiencies. The experiments described this evening are very important from my standpoint for another

reason, and this has to do with the proposal by groups of neurosurgeons to use this material in patients who have glioblastoma multiforme. I have been approached by a team of neurosurgeons who asked my advice about it, and I told them I would let them know after I had heard Dr. Wolf's paper. I am now worried about the toxic effect this material might have. I hate to think what it might do to some of the ganglion cells in the brain.

FREDERICK S. PHILIPS: For the most part I agree with what Dr. Zimmerman has said about the use of analogues of vitamins in the clarification of the functions of the vitamins. There are, however, certain complications imposed by the use of the analogues. One of the complications in the case of the analogues of nicotinamide, which are presumably converted into pseudo-coenzymes, is the possibility that such pseudo-coenzymes have variable reactivity with DPN-dependent enzymes. The fact that a false DPN is formed does not necessarily imply that it would be inhibitory. A false DPN might operate as well as natural DPN in certain enzyme systems, whereas the same pseudo-DPN could be inhibitory in still other enzyme systems. There is a further difficulty when dealing with a metabolite analogue. Here we are employing a chemical substance which is subject to specific handling by the body just as any other chemical substance is. It can be selectively stored, specifically disturbed, altered by catabolic mechanisms, and excreted by mechanisms not necessarily identical with those concerned with the pertinent metabolite. We can anticipate that such pharmacologic properties might play a major role in determining the specificity of the site of action of the antimetabolite. Moreover, one has to consider the effects of selective handling and distribution of the metabolite itself, especially where competitive antagonisms are involved. There has been a tendency on the part of biochemists who fabricate metabolite analogues to conclude too quickly that the poisonous effects of their new compounds reproduce the deficiency effect of the mimicked metabolite. I am not so convinced by some of the observations that are used to support such contentions, and I believe that, while the metabolite analogues are exceedingly valuable tools, they must be manipulated with the same degree of careful observation that is applied to elucidating the specific, selective effects of any new agent. I also want to emphasize again what Dr. Sternberg has already stated. The problem is not only explanation of what happens in cells that respond to an anti-metabolite, but, and perhaps more important, there is the question of what is the difference between one cell and another; even though both require the same metabolite, one will be destroyed while the other will not.

ANNOUNCEMENT TO FELLOWS OF THE ACADEMY

THE recommendations of The New York Academy of Medicine's Survey Committee have resulted in a recent reorganization and expansion of staff functions. The Academy welcomes three new staff members.

Dr. Aims C. McGuinness has been appointed Executive Secretary for Medical Education. He comes to us directly from Washington where for the last three years he has been Special Assistant for Health and Medical Affairs to the Secretary for Health, Education and Welfare. He has been Dean of the Graduate School of Medicine of the University of Pennsylvania, Clinical Director of ten United Mine Workers hospitals, United States delegate to World Health Assemblies, and a practicing physician in pediatrics. He succeeds Dr. Robert L. Craig, associated with the Academy since 1952, who has been appointed Executive Secretary of the Academy's new Committee on Publications and Information.

On September 1st, Mr. Robert M. Brereton was appointed to the position of Business Manager. Mr. Brereton, who is a graduate of Fordham University, has been on the administrative staff of Memorial Center for Cancer and Allied Diseases. During World War II, he served with the United States Army in the Southwest Pacific Area. Mr. Brereton succeeds Mr. Arthur A. Eberle who retired on September 1st after serving for 28 years as Comptroller of the Academy.

Mr. Thomas Leonard Stapleton came to the Academy on August 1st, as Executive Secretary of the newly-created Committee on Public Relations and Fund Raising. Mr. Stapleton has two degrees from the University of Rochester, and has had a number of years of experience in his field, in association with education, hospitals and medical research.

Dr. Iago Galdston, who has served continuously on the staff of the Academy since 1930 and as Executive Secretary of the Committee on Medical Information since its inception in 1938, has been appointed Executive Secretary of the new Committee on Special Studies.

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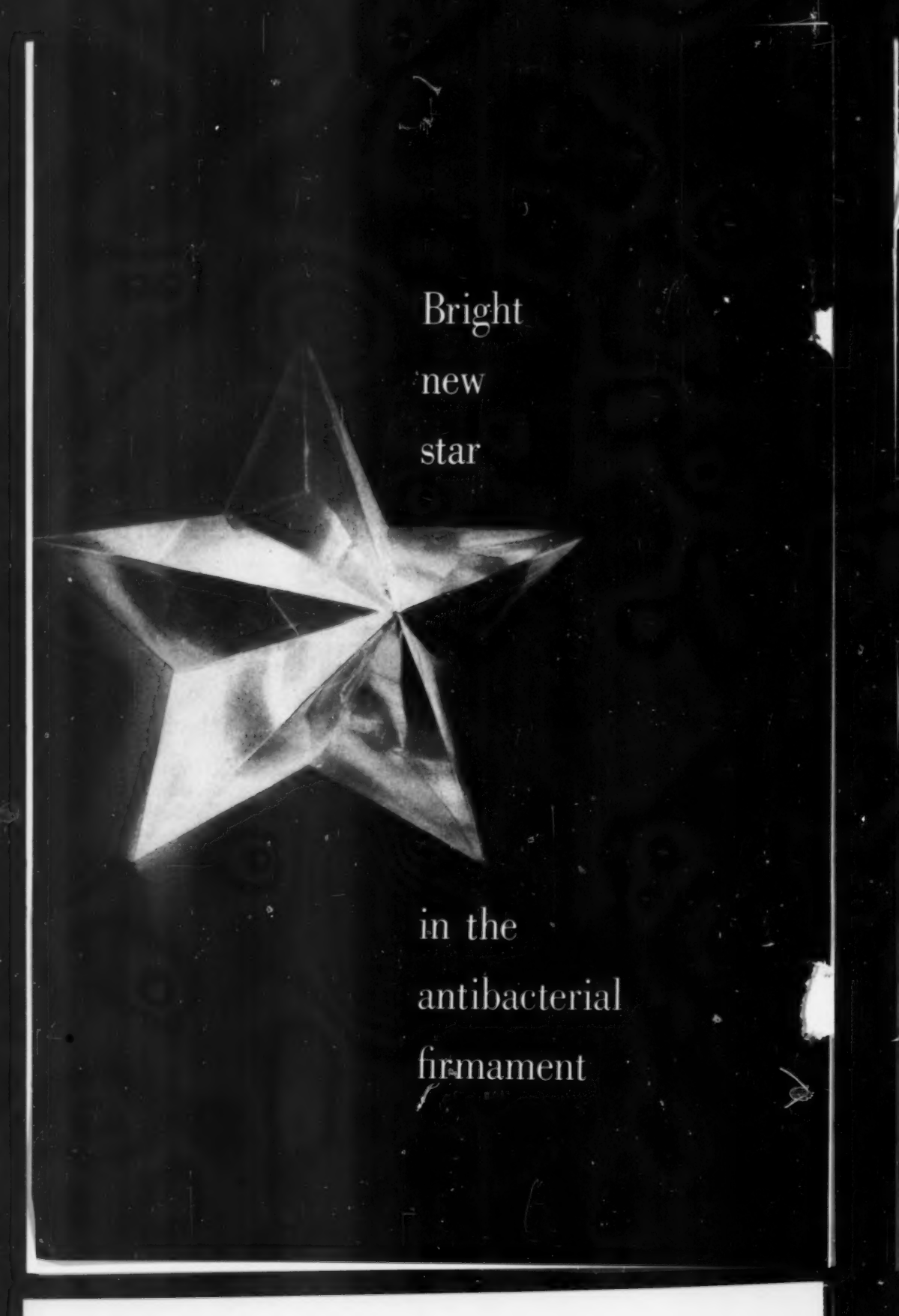
SEARLE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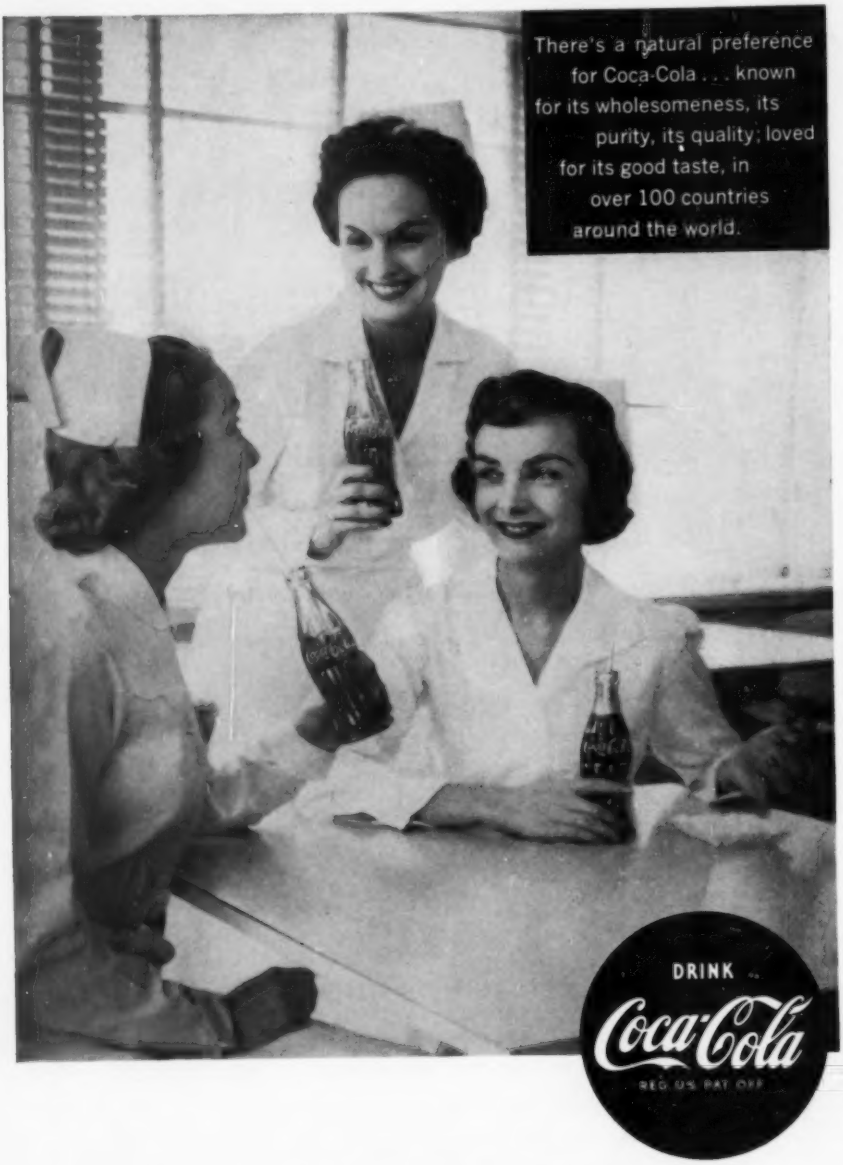

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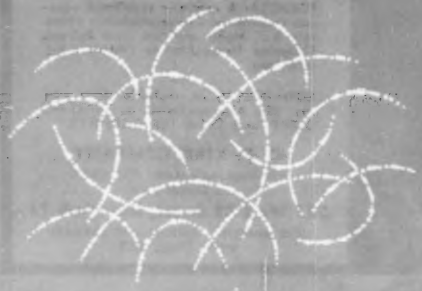

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1. Macy, I. G.; Kelly, H. J., and Sloan, R. E.: with the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks, National Academy of Sciences, National Research Council, Publication 254, Revised 1952. 2. Research Laboratories, Mead Johnson & Company.

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